CANADIAN THESES ON MICROFICHE

I.S.B.N.

THESES CANADIENNES SUR MICROFICHE

National Library of Canada
Collections Development Branch

Canadian Theses on
Microfiche Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Direction du développement des collections

Service des thèses canadiennes
sur microfiche

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

NL-339 (r. 82/08)

Canada

0-315-05926-5

National Library of Canada | Bibliothèque nationale du Canada

Canadian Theses Division | Division des thèses canadiennes

Ottawa, Canada
K1A 0N4

53846

PERMISSION TO MICROFILM — AUTORISATION DE MICROFILMER

• Please print or type — Écrire en lettres moulées ou dactylographier

Full Name of Author — Nom complet de l'auteur

SAMUEL KWADWO ATTAH-POKU

Date of Birth — Date de naissance	Country of Birth — Lieu de naissance
28th June 1948	GHANA

Permanent Address — Résidence fixe

P. O. BOX 8154, AHINSAN - KUMASI, GHANA.

Title of Thesis — Titre de la thèse

SYNTHETIC STUDIES ON ZIERONE

University — Université

UNIVERSITY OF ALBERTA

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée

Ph D

Year this degree conferred — Année d'obtention de ce grade	Name of Supervisor — Nom du directeur de thèse
1981	Dr. H. J. LIU

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

Date	Signature
10th August 1981	J. K. Attah-Poku

NL-91 (4/77)

THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON ZIERONE

by

© SAMUEL KWADWO ATTAH-POKU

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1981

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: SAMUEL KWADWO ATTAH-POKU

TITLE OF THESIS: SYNTHETIC STUDIES ON ZIERONE

DEGREE FOR WHICH THESIS WAS PRESENTED: Ph.D.

YEAR THIS DEGREE GRANTED: 1981

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed) .....

PERMANENT ADDRESS:

P.O. Box 8154

Ahinsan - Kumasi

Ghana, W. Africa

DATED August 4, 1981

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled:

SYNTHETIC STUDIES ON ZIERONE

submitted by SAMUEL KWADWO ATTAH-POKU in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

.....
Supervisor

.....

.....

.....

.....

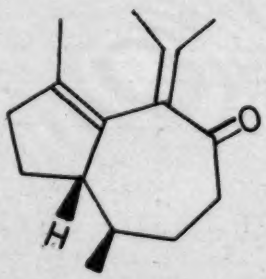
.....
External Examiner

Date: August 4, 1981

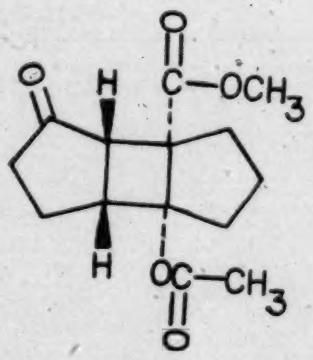
To my wife Grace and son Osei Bonsu.

ABSTRACT

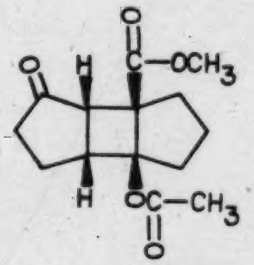
This study is directed towards the synthesis of the hydroazulenic sesquiterpene zierone (1) through the intermediacy of the photocycloadducts 101→104 and their thioketal derivatives 95→98. Photocycloaddition of 2-cyclopentenone to 1-acetoxy-2-carbomethoxycyclopentene in benzene followed by thioketalization of the inseparable adducts afforded the thioketals 95, 96, 97 and 98 in a ratio of (9.7:2.7:7.3:1) respectively and in a total yield of 62%. Hydrolysis of the thioketal moieties of these compounds afforded the corresponding ketones, the original photocycloadducts 103, 102, 104 and 101. Repetition of the photocycloaddition reaction in isopropanol afforded the keto-diesters 101 and 103 in a ratio of 5:1 and in a total yield of 50%. The structures and stereochemistry of these compounds were elucidated through chemical transformations and the results are detailed in Chapter II of this thesis.



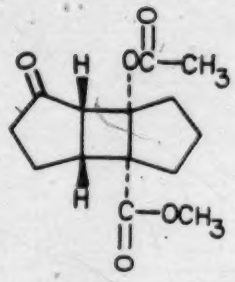
1



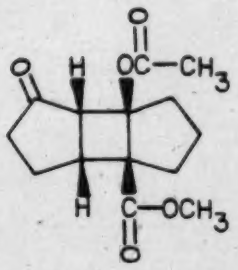
101



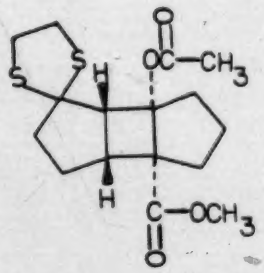
102



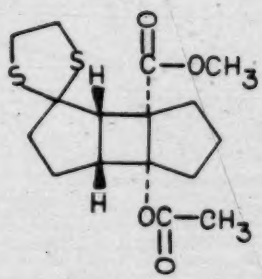
103



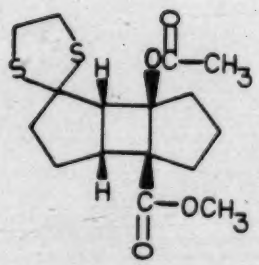
104



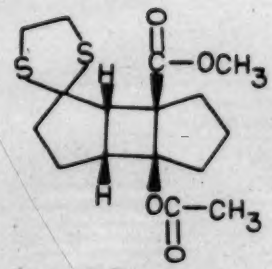
95



96

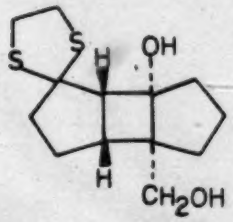


97

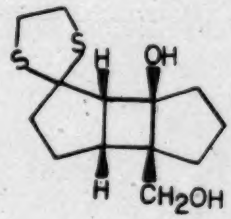


98

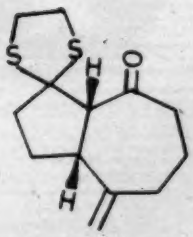
Towards the synthesis of zierone (1), the thioketal-diesters 95 and 97 were reduced with lithium aluminum hydride to afford the corresponding diols 105 and 117, which were treated with p-toluenesulfonyl chloride to afford the hydroazulenone 106. Various efforts made to convert 106 into 139, an envisaged precursor of zierone are presented. In a closely related approach, the keto-diesters 103 and 104 were treated with methyllithium and the products were subjected to sodium methoxide treatment to give the functionalized hydroazulenes 126 and 130. Treatment of 126 and 130 with 1,2-ethanedithiol afforded the corresponding thioketals 161 and 160, the ester functionalities of which were reduced with lithium aluminum hydride. The resulting alcohols 164 and 165 were treated with p-toluenesulfonyl chloride and the resulting toluenesulfonates 166 and 167 were reductively cleaved with lithium aluminum hydride. Hydrolysis of the thioketal groups of the reduction products 168 and 169 with mercuric chloride afforded the versatile hydroazulene sesquiterpene precursors 131 and 132 with defined stereochemistry. Attempts to convert 131 into zierone (1), the target molecule of these studies, are also discussed.



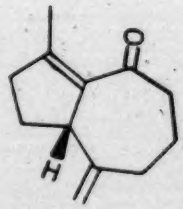
105



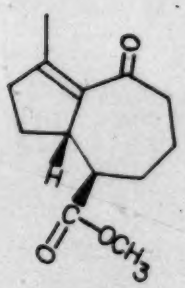
117



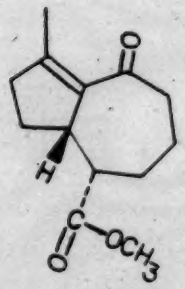
106



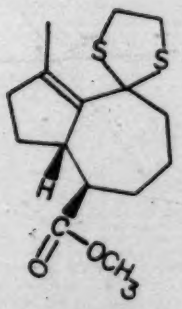
139



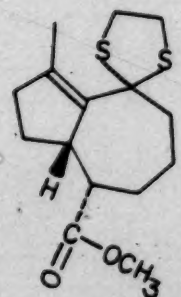
126



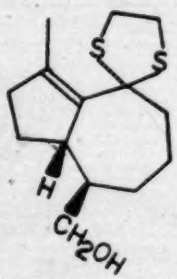
130



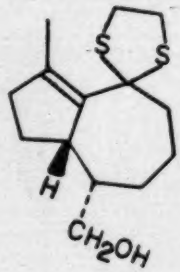
161



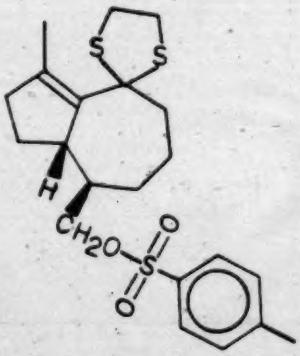
160



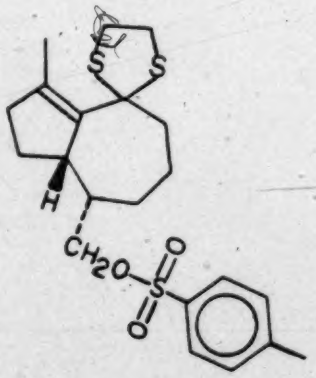
164



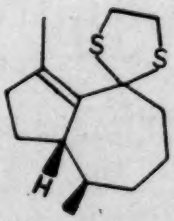
165



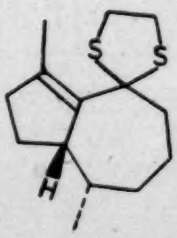
166



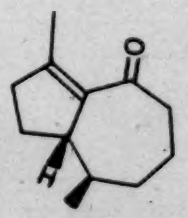
167



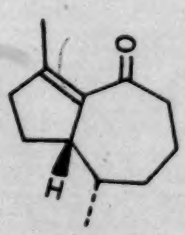
168



169



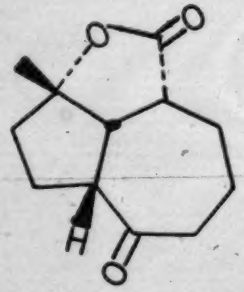
131



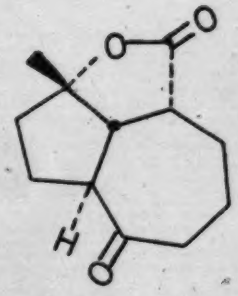
132

In another approach, the keto-diesters 101 and 102 were treated with methyllithium and the intermediate products were treated with sodium methoxide to give the keto-lactones 136 and 137. These compounds were converted stereoselectively into the lactones 193 and 194 as follows. Treatment of 136 and 137 with methoxymethylenetriphenylphosphorane afforded the methyl vinyl ethers 187 and 188, hydrolysis of which with aqueous hydrochloric acid gave the aldehydes 189 and 190. Thioketalization of the aldehydes with 1,2-ethanedithiol gave the thioketals 191 and 192, which were reductively cleaved with Raney nickel (W-2) to give the keto-lactones 193 and 194. The stereochemistry of 193 and 194 were proven by their conversion into 131, thus treatment of 194 with methyllithium and 193 with methylmagnesium bromide afforded the respective hemiketals 203 and 207 which were dehydrated with sulfonic acid to give the cyclic ethers 204 and 208. Sequential treatment of these ethers with ozone, methyl sulfide and sodium methoxide afforded 131. The lactone 193 was converted into the enone 229, a potential synthetic precursor of zierone, as follows. Sequential treatment of 193 with lithium diisopropylamide, benzeneselenenyl chloride and hydrogen peroxide gave the unsaturated lactone 219. Epoxidation of 219 with hydrogen peroxide followed by treatment of the product with methyllithium gave the corresponding epoxy-hemiketal which was methylated to give the epoxy-ketal 227. The lactone 194 was similarly converted into the isomeric epoxy-ketal 228.

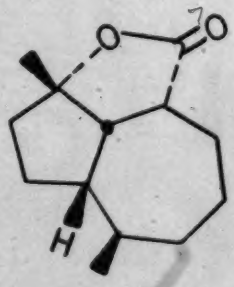
On treatment with boron trifluoride etherate, the epoxy-ketal underwent rearrangement with concomitant elimination of methanol to give the enone 229.



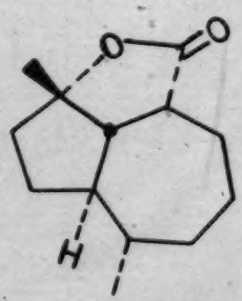
136



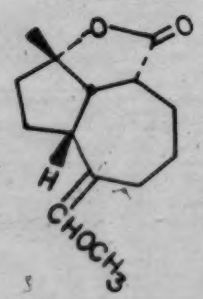
137



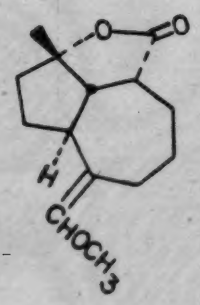
193



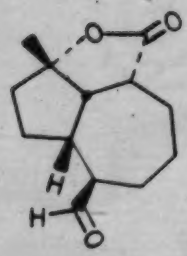
194



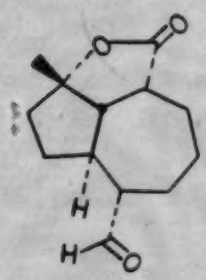
187



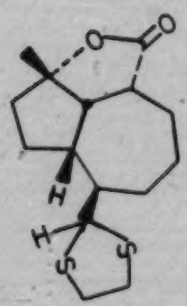
188



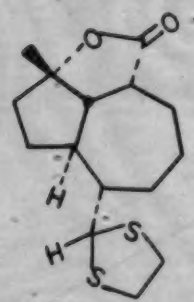
189



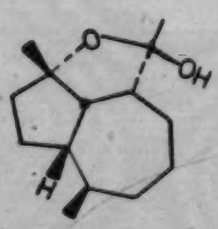
190



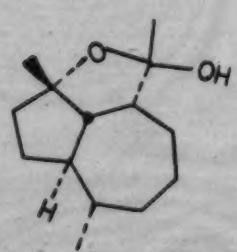
191



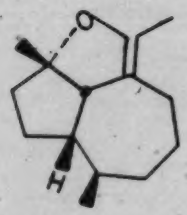
192



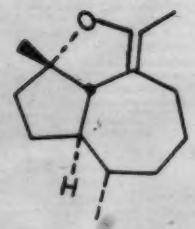
203



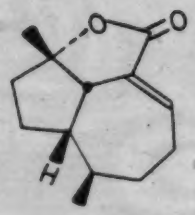
207



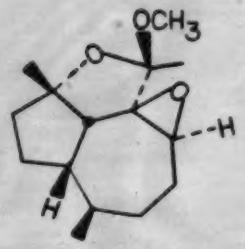
204



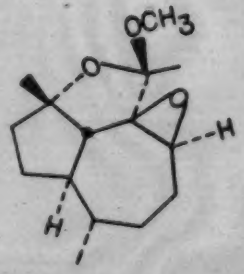
208



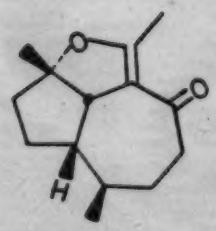
219



227



228



229

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to:

Dr. H.J. Liu for his role as a research director during the course of these studies, and the preparation of this thesis.

Dr. A.S. Kwesi Aidoo, a former student of this department, who assisted in many ways towards my coming to this department.

Dr. A.M. Hogg, Dr. T.T. Nakashima, Mr. R.N. Swindlehurst and their associates for their respective roles in recording the mass and pmr sepctra and the microanalysis work.

The staff of the research stores, the glass blowing unit, and the various technical services.

The entire teaching staff of this department for their invaluable examples as teachers.

The National Research Council of Canada, and also The Government of Ghana through the University of Science and Technology, Kumasi for financial support, and to Mrs. Sarita Kale for typing this thesis.

TABLE OF CONTENTS

	Page
Abstract	v
Acknowledgement	xiv
List of Schemes	xvi
List of Figures	xvii

SYNTHETIC STUDIES ON ZIERONE

CHAPTER		Page
I.	INTRODUCTION	1
	RESULTS AND DISCUSSION	33
II.	PHOTOCYCLOADDITION OF 2-CYCLOPENTENONE AND 1-ACETOXY-2-CARBOMETHOXYCYCLOPENTENE AND STRUCTURAL ELUCIDATION OF ADDUCTS	34
III.	APPROACHES TO ZIERONE VIA THE HEAD-TO-HEAD PHOTOCYCLOADDUCTS	72
IV.	APPROACH TO ZIERONE VIA THE HEAD-TO-TAIL PHOTOCYCLOADDUCTS	112
V.	EXPERIMENTAL	152

***

REFERENCES 226

LIST OF SCHEMES

	Page
Scheme I	31
Scheme II	45
Scheme III	68
Scheme IV	69
Scheme V	74
Scheme VI	75
Scheme VII	107
Scheme VIII	115

LIST OF FIGURES

	Page
Formula 1 to 6	3
Formula 7 to 12	5
Formula 13 to 18	7
Formula 19 to 24	9
Formula 25 to 30	11
Formula 31 to 36	15
Formula 37 to 42	16
Formula 43 to 48	17
Formula 49 to 54	18
Formula 55 to 60	20
Formula 61 to 66	22
Formula 67 to 72	23
Formula 73 to 78	25
Formula 79 to 84	27
Formula 85 to 90	29
Formula 91 to 96	30
Formula 97 to 100b	37
Formula 100c to 104	38
Formula 105 to 110	41
Formula 111 to 116	49
Formula 117 to 121	51
Formula 122 to 127	55
Formula 128 to 133	59
Formula 134 to 139	65

	Page
Formula 140 to 144a	78
Formula 145 to 149a	80
Formula 150 to 155	84
Formula 156 to 161	86
Formula 162 to 167	92
Formula 168 to 173	100
Formula 174 to 179	102
Formula 180 to 183b	110
Formula 184a to 185	111
Formula 186 to 190	121
Formula 190a to 195	124
Formula 196 to 201	128
Formula 202 to 207	133
Formula 208 to 213	135
Formula 214 to 219	140
Formula 220 to 225	142
Formula 226 to 231	147
Formula 232 to 237	149
Formula 238	150

***

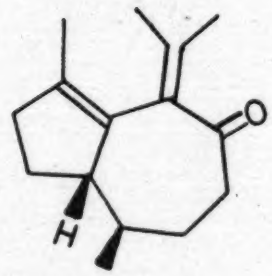
Figure 1	151

CHAPTER I: INTRODUCTION

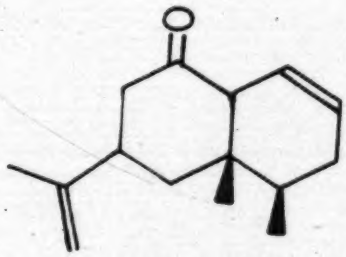
Zierone (1),* a hydroazulenic sesquiterpene ketone, was first isolated in 1926 by Penfold[1] from Zieria macrophylla. Investigation by Bradfield, Penfold and Simonsen[2,3] led to the assignment of the molecular composition of $C_{15}H_{20}O$, isomeric with the then known eremophilone (2). No structural assignments were made for zierone until nearly two decades later when renewed investigations on zierone by Birch, Collins and Penfold[4] showed it to be a bicyclic compound. From its infrared and ultraviolet spectra, it was shown to contain an α,β-unsaturated ketone moiety and another double bond. Reduction and dehydrogenation of zierone gave a new violet azulene, zierazulene (3), while α-formylation of zierone followed by reduction and dehydrogenation yielded a tetraalkylazulene (4) in which the newly introduced methyl group was in a position adjacent to that previously occupied by the ketone group. An unambiguous synthesis of 2,4-dimethyl-8-isopropylazulene (4) confirmed these structural assignments.[5] On the basis of this structural assignment, the isoprene rule and other chemical evidence, the structure 5 was suggested for zierone. Hildebrand and Sutherland[6] later confirmed the presence of an α,β-unsaturated ketone functionality. They also found that ozonolysis of zierone produced acetone as

---

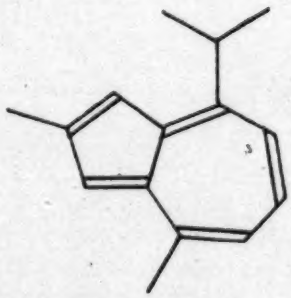
* The ring system is numbered according to the convention of hydroazulenes. This nomenclature is used for all the bicyclo[5.3.0] systems in this text.



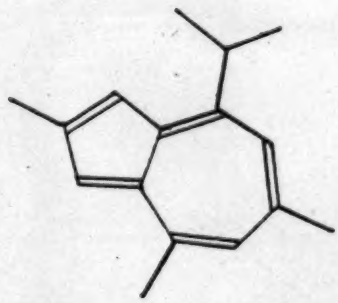
1



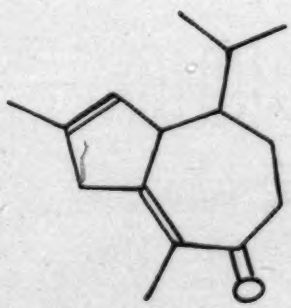
2



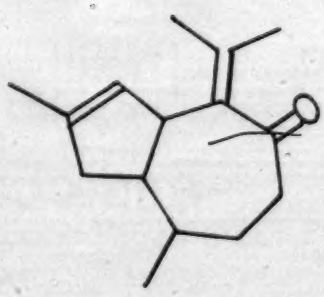
3



4



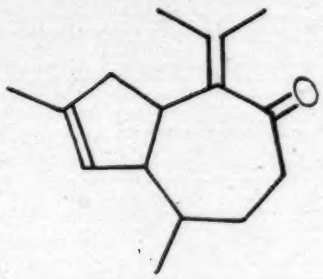
5



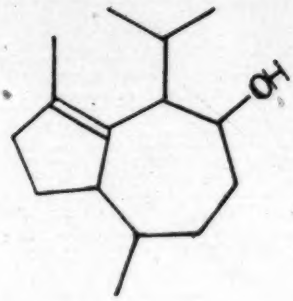
6

one of the fragments and that acetone was also produced on heating zierone with aqueous ethanolic potassium hydroxide. These results indicated clearly that zierone contains an isopropylidene group which is in conjugation with the ketone functionality. These findings led to a modification of the previously assigned structure of zierone to 6 or 7. These investigators also showed that zierone was identical with elleryone isolated from Evodia elleryana by Jones and Wright[7] in 1946.

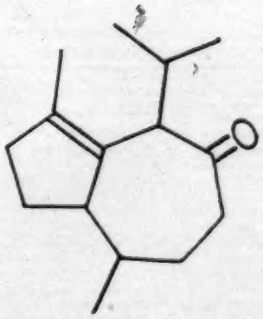
More recently Barton and Gupta[8,9] showed that all of the above structures 5, 6 and 7 were incorrectly assigned. They eliminated the possibilities of a C-2 or a C-3 double bond due to the absence of vinylic protons as evident from the proton magnetic resonance (pmr) spectrum of zierone. Reduction of zierone with sodium in ethanol gave dihydrozierol (8) confirming that the isopropylidene double bond is in conjugation with the ketone carbonyl. The 3,5-dinitrobenzoate of dihydrozierol (8) showed in its pmr spectrum signals indicating the presence of an isopropyl and a vinylic methyl groups as well as a $CH_3\overset{|}{C}H-$ moiety. Jones' oxidation of the dihydrozierol afforded dihydrozierone (9) which had a UV maximum at 294 mμ (ε 330), indicative of an β,γ-unsaturated ketone system.[10] Reduction of zierone with lithium aluminum hydride afforded zierol (10), the pmr spectrum of which showed signals indicating the presence of three vinylic methyl groups and a $CH_3\overset{|}{C}H-$ moiety. The observed ultraviolet spectrum of the 3,5-dinitrobenzoate



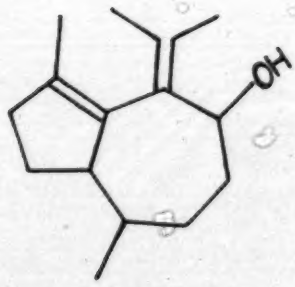
7



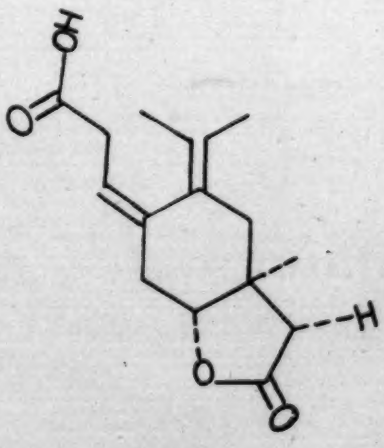
8



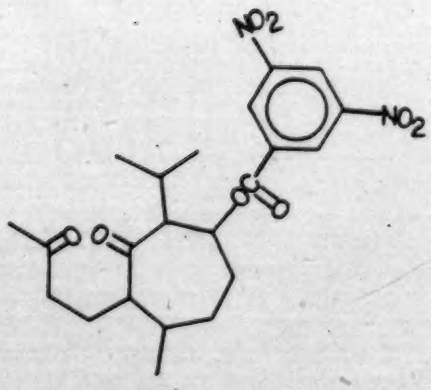
9



10



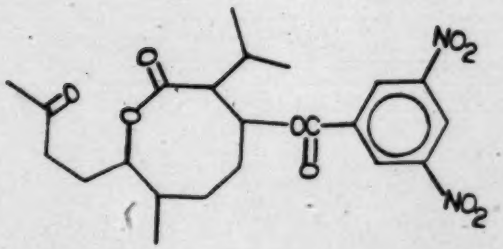
11



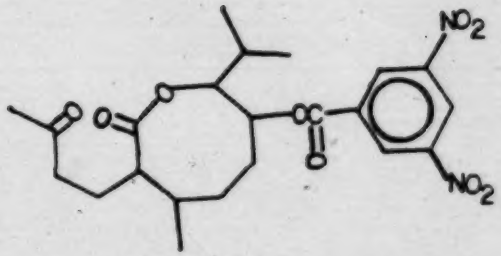
12

of 10 after subtraction of the spectrum of cyclohexyl-3,5-dinitrobenzoate led to the conclusion that zierone contains a conjugated diene system of abnormal (overcrowded) type such as is found in photosantonic acid (11). Ozonolysis of the 3,5-dinitrobenzoate of 8 yielded two crystalline products identified as 12 and 13 or 14, both of which were methyl ketones as shown by their pmr spectra. The diketone 12 was also obtained by ozonolysis of 8, followed by esterification of the resulting hydroxy diketone 15 with 3,5-dinitrobenzoyl chloride. These observations led to the conclusion that zierone possesses the gross structure shown in formula 1.

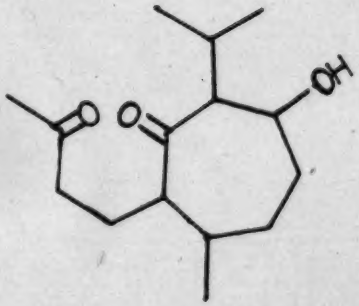
Birch, Collins, Penfold and Turnbull[11] obtained more extensive evidence which led independently to the same structural assignment for zierone. The environment of the carbonyl group was explored by treatment of hydroxymethylene zierone (16) with hydrogen peroxide. This afforded a dicarboxylic acid, $C_{15}H_{24}O_4$, which was shown to possess the structure 17. Reduction of 17 with sodium in butanol gave a dihydroderivative, $C_{15}H_{26}O_4$, which showed a much less intense ultraviolet absorption at λmax 210 mμ (ε 6400) compared to that of 17 at λmax 210 mμ (ε 10550) in agreement with the reduction of an α,β-unsaturated acid system. On treatment with osmium tetraoxide, zierone was converted into dihydrodihydroxyzierone, $C_{15}H_{24}O_3$. Although this compound showed the expected infrared bands at 3268, 1690 and 1647 cm^{-1} (nujol), it had an unexpectedly weak band in the



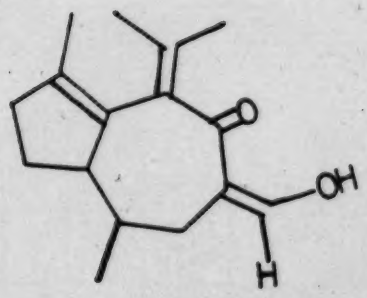
13



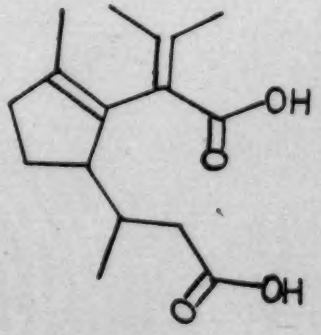
14



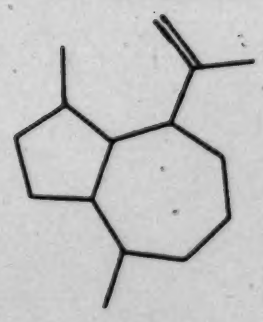
15



16



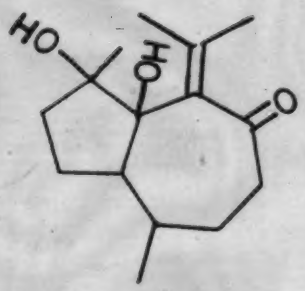
17



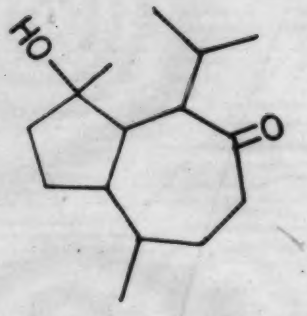
18

ultraviolet spectrum [λmax 246 mμ (ε 2540) in ethanol or light petroleum]. At this point it was noted that zierone itself has an ultraviolet maximum at a somewhat lower wavelength (245 mμ) than the expected value of about 252 mμ. The low intensity of the dihydrodihydroxyzierone band was explained by the presence of a C-4 but not a C-3 methyl group in zierone. The necessary migration of the methyl group to the C-3 position during dehydrogenation leading to the azulene 3 could be explained by steric congestion and is strongly supported by the observation that the hydrocarbon 18 derived from aromadendrane gives zierazulene 3 on dehydrogenation. Consequently dihydrodihydroxyzierone was assigned structure 19. The final confirmation was obtained from examination of the reactions of 19. Reduction of 19 with lithium in liquid ammonia gave a mixture of ketonic products one of which was the ketoalchohol 20. Reduction of 19 with lithium aluminum hydride gave the triol, $C_{15}H_{26}O_3$, which on treatment with lead tetraacetate gave the expected hydroxydiketone 21 containing a new unsaturated grouping. Fission of dihydrodihydroxyzierone 19 gave the expected product 22. These results coupled with spectral data led to the assignment of the gross structure of zierone as 1.

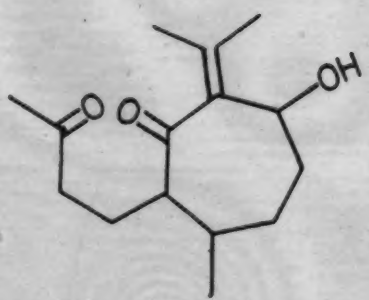
The stereochemistry of zierone remained unknown until recently when Ito et al.[12,13] obtained 10-epizierone (26) from gurjenene (23). Sensitized photooxygenation of gurjenene, followed by sodium borohydride reduction of the resulting hydroperoxide afforded the allylic alcohol 24.



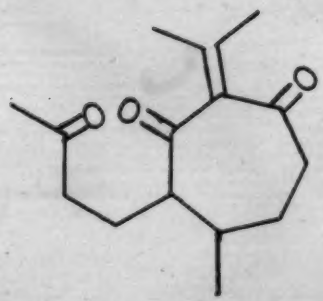
19



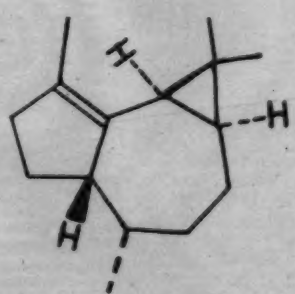
20



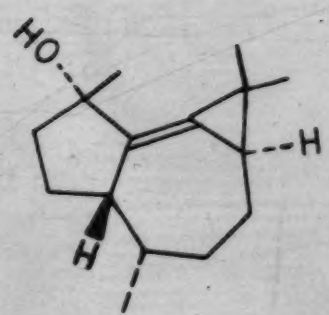
21



22



23

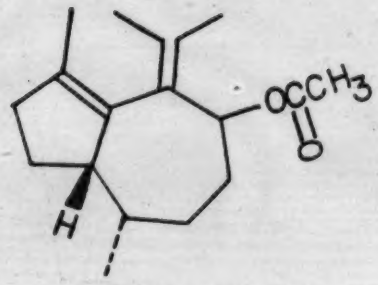


24

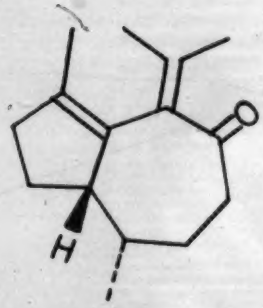
Treatment of 24 with oxalic acid in acetic anhydride resulted in the skeletal rearrangement to yield 10-epizieryl acetate (25). Lithium aluminum hydride reduction of 25 gave the corresponding alcohol which was oxidized with chromium trioxide - pyridine to 10-epizierone (26). This compound and zierone (1) were shown spectroscopically to be non-identical. The sign of the Cotton effect in the circular dispersion diagrams of 26 and 1 were found to be the same suggesting that the chirality of the π-electron system and therefore the configuration at C-1 is the same in both compounds, thus they are epimeric at C-10. Since the absolute stereochemistry of gurjenene (23) had been shown by Palmade[14] to be the 1R, 10R-configuration, zierone was assigned the 1R, 10S-configuration.

The most commonly occuring hydroazulenic sesquiterpenoids possess the guaiazulenic skeleton 27. From the biogenetic point of view these naturally occurring sesquiterpenoids are considered as possessing the "normal skeleton" arising from farnesyl pyrophosphate. A group of closely related sesquiterpenoids known as pseudoguaiazulenes have rearranged carbon skeleton 5 in which the C-4 methyl group has migrated to the C-5 position. A third class is the so-called "zierazulene" family possessing a rearranged guaiazulene skeleton in which the isopropyl rather than the methyl group has migrated to the C-6 position, and the only known member in this family is zierone (1).

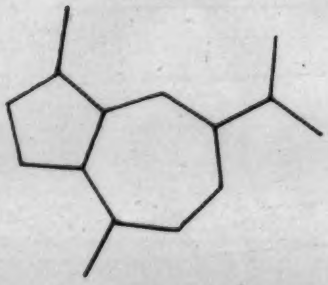
Interest in hydroazulenic compounds has been extensive



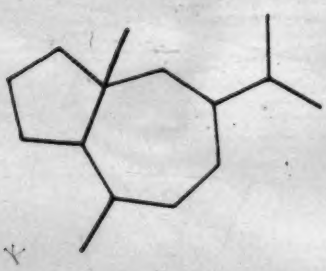
25



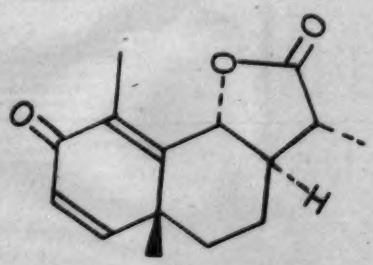
26



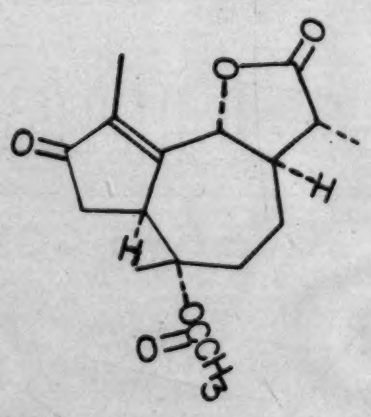
27



28



29



30

and is steadily growing mainly because many of them are useful as aromachemicals and many of these compounds have marked antitumour and antibacterial properties.[14-17] Furthermore, the structural diversity and complexity found in the hydroazulenic sesquiterpenoid group of compounds have served as intriguing attractions towards the development of new and efficient synthesis of these compounds.

Our interest in the studies towards the total synthesis of zierone (1) stems from a number of reasons. It is the only known member of the zierazulene family which is naturally occuring and possesses an unique hydroazulenic carbon skeleton. Moreover it has an unusual cross-conjugated dienone system which is considered to be synthetically challenging in view of the sterically crowded nature of the environment of this system. It is also noted that zierone has not yet been synthesized, consequently an unambiguous total synthesis will confirm its structural and stereochemical assignments.

In general there are two basic problems associated with the synthesis of hydroazulenic sesquiterpenes. The first problem is the control of stereochemistry. This arises from the fact that little information is available to date on the conformational analysis of the cyclopentane[18,19] or cycloheptane[18,20-24] systems, thus making conformational predictions on the bicyclo[5.3.0]decane system difficult, and that reactions on this system often lead to gross mixtures of all possible diastereoisomers due

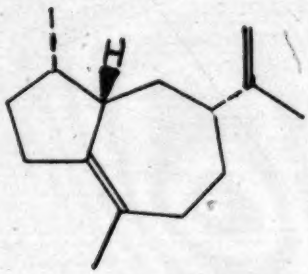
to the conformational flexibility of the cycloheptane ring. In the case of zierone however, this stereochemical control does not pose a serious problem as there are only two chiral centres. The second general problem is the construction of a suitably functionalized hydroazulenic system which can be subsequently elaborated to afford the desired compound. This requirement is apparently the more formidable task in the case of zierone.

In recent years extensive attention has been drawn towards the synthesis of the hydroazulenic system and a number of methods have been developed. The existing methods can be generally classified into the following four categories.

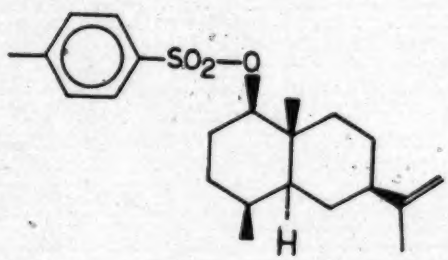
(a) Rearrangement of bicyclic systems containing cyclohexane rings, especially the bicyclo[4.4.0]decane derivatives due to their ready accessibility. Examples in this category include the photochemical conversion of santonin (29) into isophotosantonic lactone (30) by Barton, de Mayo and Shafig.[25] Solvolytic rearrangement of bicyclo[4.4.0]-decane derivatives has been utilized in the formation of the hydroazulene skeleton by Heathcock et al.[26] in the synthesis of α-bulnesene (31). Thus, treatment of the tosylate 32 with potassium acetate in acetic acid afforded α-bulnesene (31). A variation of this solvolytic procedure which facilitates the rearrangement of bicyclo[4.4.0]decanes to hydroazulenes involves the pinacolic-type rearrangement of vicinal hydroxysulfonates under mild basic conditions.[27-31]

For example, the key step in the synthesis of dl-pogostol (33) by Vig et al.[32] was the rearrangement of the α-hydroxytosylate 34 to the ketone 35 using potassium tertiary butoxide in tertiary butanol. This approach has also been used by Buchi et al.[30] in the synthesis of aromadendrane (36) involving the rearrangement of the hydroxytosylate 37 as the key step. The solvolytic rearrangement of bicyclo-[4.4.0]decenones has also been utilized as a route to hydroazulenes, as exemplified by the rearrangement of the enone 38 with silver sulfate in sulfuric acid to afford the pseudoguainolide skeleton 39.[33] As a final example in this category, ozonolysis of the octaline 40 produced the intermediate diketone 41, which upon base treatment cyclized to give the hydroazulene 42. This methodology has been successfully employed by Kretchner et al.[34] in the synthesis of dl-damsin (43) using a suitably functionalized octalone derivative 44.

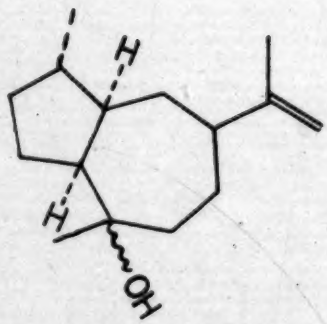
(b) Cation-initiated olefin cyclization of appropriately functionalized cyclopentane derivatives. Marshall and Andersen[35,36] demonstrated that upon treatment with stannic chloride, the olefinic aldehydes 45 and 46 underwent cyclization to give the hydroazulenes 47 and 48 respectively in a highly stereoselective manner. This approach has been successfully utilized in the synthesis of β-kessanol (49).[37] It has also been shown to be applicable to the synthesis of pseudoguainolides as exemplified by the synthesis of confertin (50) by Semmelhack et al.[38] In this



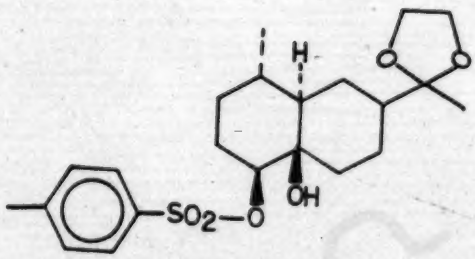
31



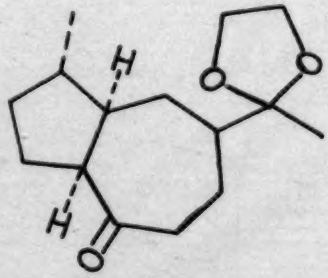
32



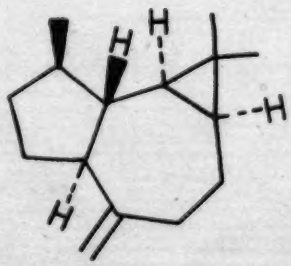
33



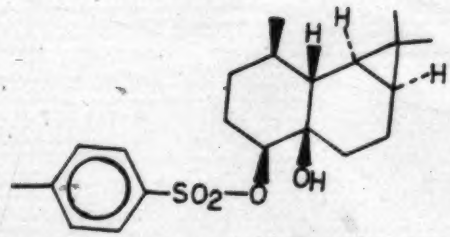
34



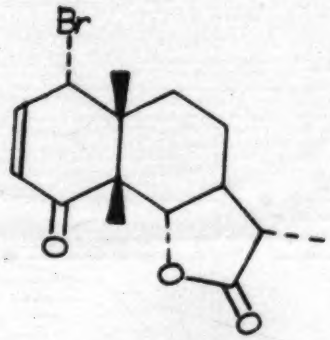
35



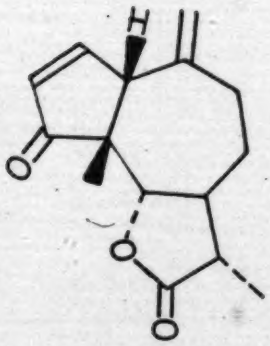
36



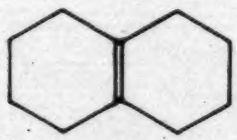
37



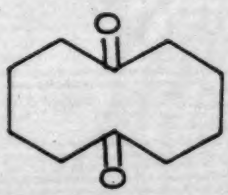
38



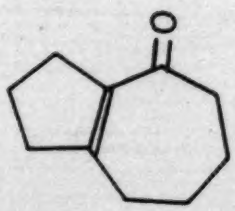
39



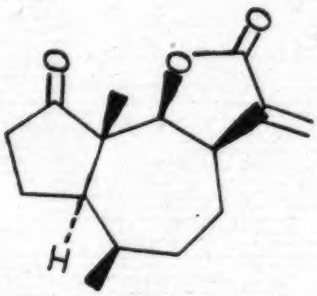
40



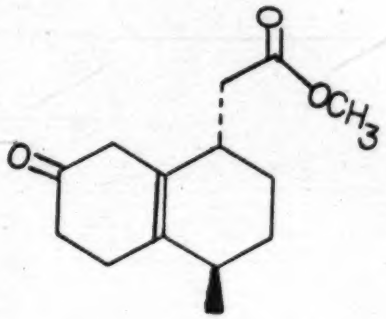
41



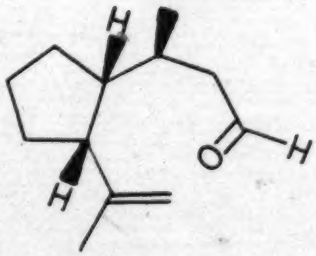
42



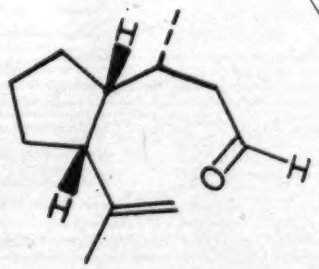
43



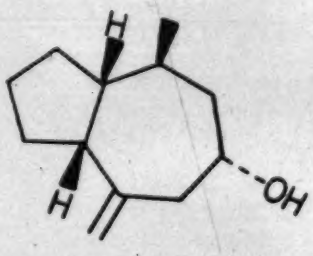
44



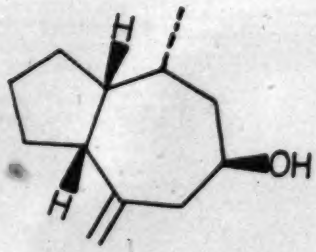
45



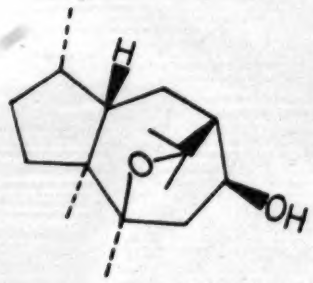
46



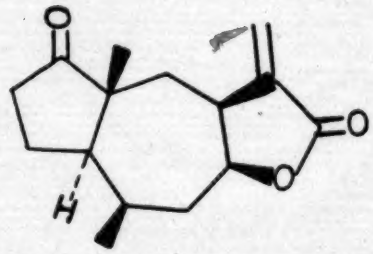
47



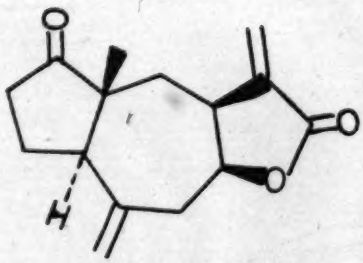
48



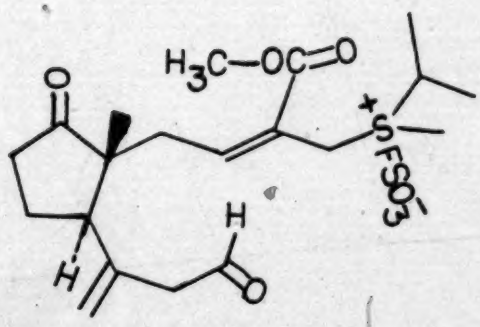
49



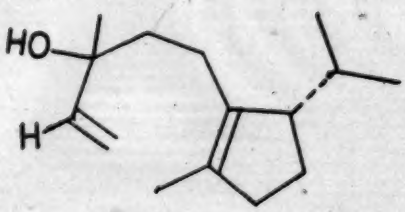
50



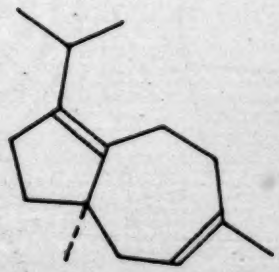
51



52



53



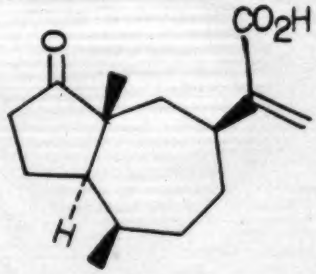
54

synthesis the formation of the hydroazulene 51 was achieved by the cyclization of the olefinic aldehyde 52 with (1,5-cyclooctadiene) Ni(0). An alternative procedure which encompasses acid catalyzed cyclization of a suitable polyenic compound instead of a Prins reaction discussed previously has been extensively used in the stereoselective synthesis of hydroazulenes.

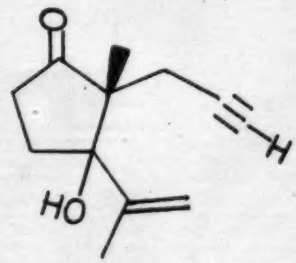
The cyclization of the dienol 53 induced by formic acid at room temperature to give (-)-daucene (54)[39] is an example of this class of cyclization reactions. This methodology has also been used by Harding and Nash[40] in the synthesis of the pseudoguainolide damsinic acid (55) via formic acid catalyzed cyclization of 56 to afford the intermediate hydroazulenic-dione 57.

(c) Intramolecular alkylation or aldol condensation of properly functionalized cyclopentane derivatives. Using such an approach Grieco et al.[41] have successfully completed the total synthesis of (dl)-damsin (58) and (dl)-ambrosin (59) via the intermediacy of the keto-iodide 60, which was cyclized to the ketone 61 upon treatment with lithium hexamethyldisilylazide. A recent example in this class involved the intramolecular aldol condensation of the keto-aldehyde 62 with potassium hydroxide to give the enedione 63 which was subsequently converted to dl-helenalin (64).[42]

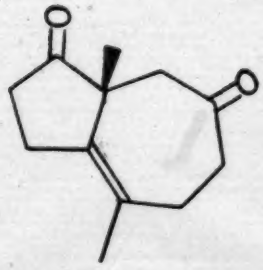
(d) Cleavage of tricyclic compounds which embodies a bicyclo[5.3.0]decane moiety. Sodium hydroxide induced fragmentation of the tricyclic ketone 65 prepared from the



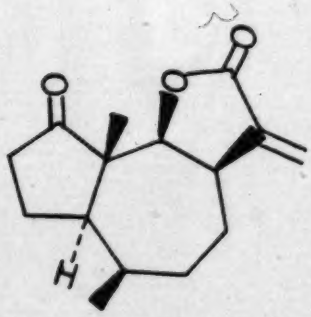
55



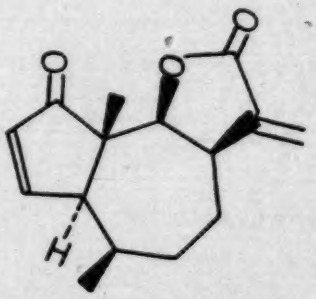
56



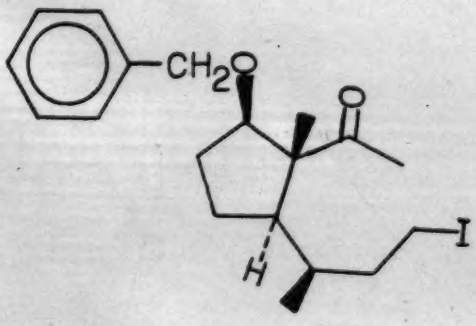
57



58

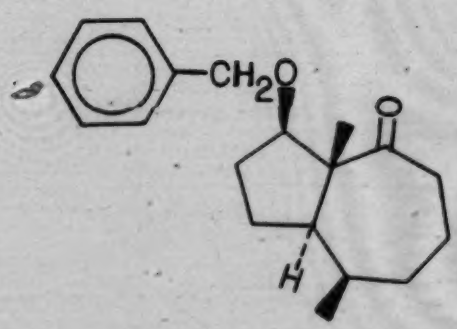


59

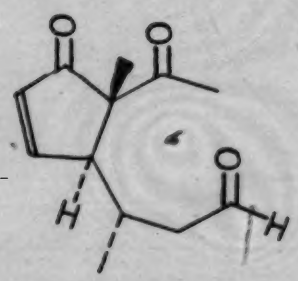


60

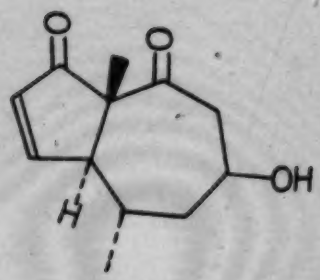
aldehyde 66 and the enamine 67 to give the acid 68[43] and the sodium methoxide promoted cleavage of the tricyclic enedione 69 to the hydroazulenic derivative 70[44] are versatile examples in this category. The base induced cleavage of a specific bond 'a' or 'b' in an appropriate tricyclo[5.3.0.$0^{2,6}$]decane derivative 71 could also in principle generate the hydroazulenic skeleton. This type of synthetic approach has been facilitated by the rapid development of photocycloaddition reactions in recent years and is employed as a route to the hydroazulenic skeleton in this work. Hikino and de Mayo[45] first demonstrated the feasibility of such an approach. The photochemical cycloaddition of cyclopentene and 3-acetoxy-2-cyclopentene-1-one gave the otherwise difficultly accessible tricyclic compound 72. This adduct provided adequate functionalities for the selective bond cleavage via a retroaldol reaction resulting in the formation of the dione 73. Such an approach clearly has an advantage over the other known procedures previously discussed in terms of its simplicity. The above particular example however, has limited applications to the synthesis of naturally occurring hydroazulenic compounds due to the expected difficulty in differentiating between the two ketone carbonyls and the complete lack of functionality in the five-membered ring necessary for its subsequent modification. Although in principle, the required substituents in the five membered ring can be introduced using substituted cyclopentene as a starting material in



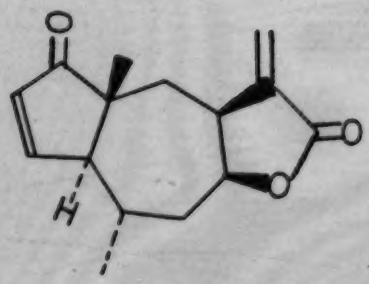
61



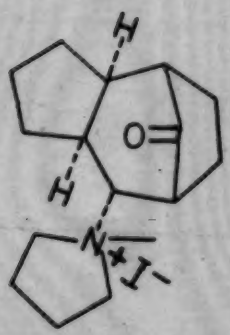
62



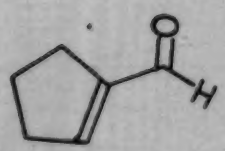
63



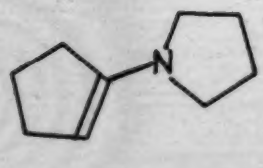
64



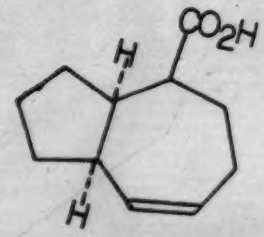
65



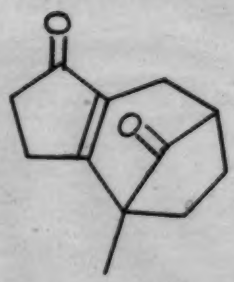
66



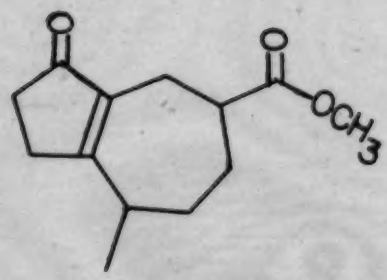
67



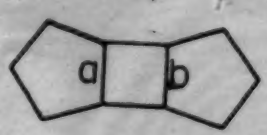
68



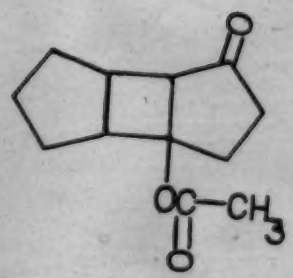
69



70

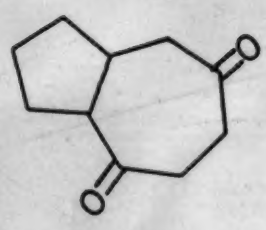


71

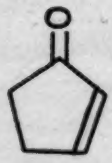


72

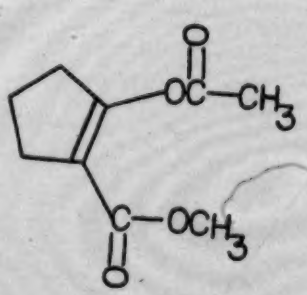
the photocycloaddition reaction, practically, it is not feasible unless a symmetrically substituted cyclopentene is used. This is as a result of the expected difficulty in controlling the orientation of the photochemical process involving an unsymmetrically substituted cyclopentene. In light of this problem, a modified version leading to a hydroazulenic system containing adequate groupings in both rings has been developed.[46] In this modification the intermediate tricylic compound 76 was prepared with high regioselectivity by photocycloaddition of 2-cyclopentene-1-one (74) to 1-acetoxy-2-carbomethoxycyclopentene (75). The two substituents on 75 were expected to reinforce the regioselectivity of the cycloaddition since they had been shown to exert opposite orientational effects.[47,48] Their relative locations in the photocycloadduct 76 were furthermore expected to facilitate the cleavage of a specific bond by a reverse Claisen-type reaction leading to the hydroazulene skeleton. Thus treatment of 76 with sodium methoxide gave the diketone 77. Alternatively ketalization of 76 with ethylene glycol, followed by treatment with sodium methoxide resulted in the formation of the keto-ester 78 thereby allowing an easy differentiation of the two ketone carbonyls. Although the same general principle applies these two photochemical approaches have practical differences. Most noticeably, in the latter case the cyclopentanone ring was retained in the final hydroazulene skeleton while in the former case it was modified to a seven-membered ring. The



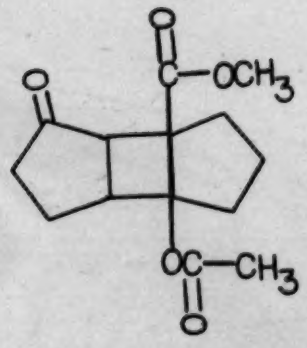
73



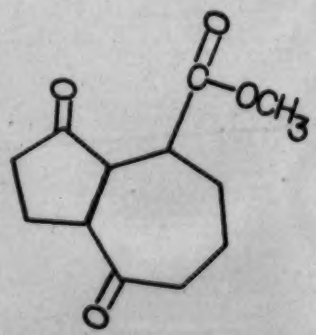
74



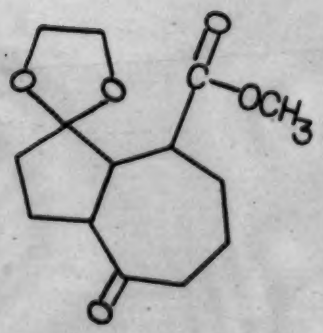
75



76



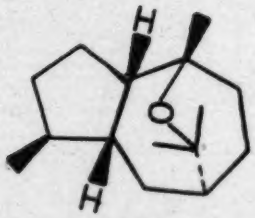
77



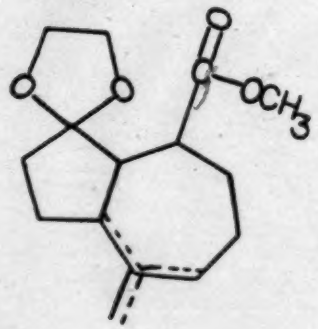
78

applicability of the latter method towards the synthesis of sesquiterpenes has been demonstrated by Liu and Lee[49] in the synthesis of 5-epikessane (79).

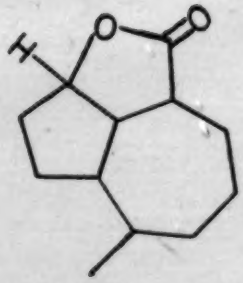
Keto-ester 78 is of considerable use as an intermediate for the synthesis of zierone (1) by virtue of the fact that the existing functional groups are appropriately located for further introduction of substituents and functionalities. It can be seen that the three alkyl groups of zierone (1) coincide with the locations of the existing functional groups in the keto-ester 78. It is therefore conceivable that the carbon skeleton of zierone (1) could be obtained by the appropriate transformations of 78. In this connection preliminary investigations have been carried out using 78.[50] Grignard reaction of the keto-ester 78 with methylmagnesium bromide followed by dehydration of the intermediate alcohol with phosphoryl chloride in pyridine afforded an isomeric mixture of olefins 80. Attempted catalytic hydrogenation of the double bond under various conditions however resulted in the formation of a substantial quantity of the undesirable lactone 81. As a consequence of these results the more stable thioketal 82 was prepared in order to pursue the synthesis of zierone in this direction. Corleto[51] prepared the photocycloadducts by prolonged irradiation of 2-cyclopentene-1-one and 1-acetoxy-2-carbomethoxycyclopentene in benzene. The photocycloadducts were subsequently treated with 1,2-ethanedithiol in the presence of boron trifluoride etherate. After column



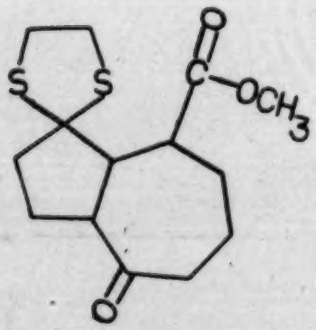
79



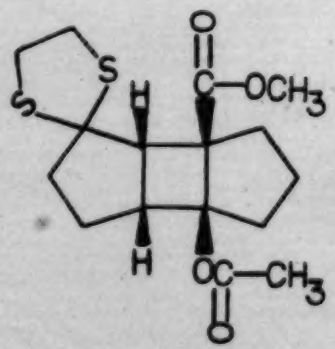
80



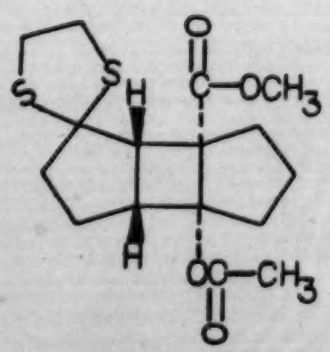
81



82



83

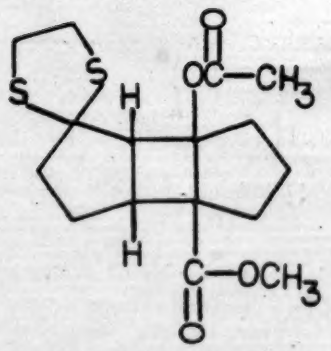


84

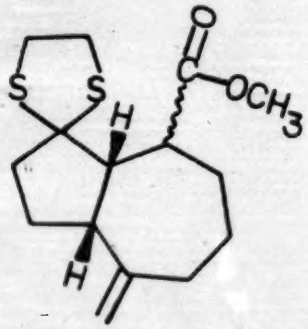
chromatography on silica gel the products were separated to give two fractions in a ratio of 4:1 in a total of 68% overall yield. The major fraction which was faster moving on silica gel thin layer chromatography (tlc) was shown to consist of two compounds to which structures 83 and 84 were assigned.* On the basis of the available information structure 85 was further assigned to a crystalline compound isolated from the minor fraction. Treatment of the major fraction with sodium methoxide in methanol gave a diastereomeric mixture containing at least three keto-esters 87 in 53% yield. A successful effort was made to introduce the C-10 methyl group of zierone (1) into 82. Wittig reaction of 82 with methylenetriphenylphosphorane[52] afforded a mixture of diastereomeric olefins 86 (10% yield) and 87 (60% yield). Catalytic hydrogenation of these compounds using ten-fold excess (by weight) of 5% palladium on carbon gave a single product 88 from 86 and two products, 89 and 90 from 87. A fourth isomer 91 was obtained by a different route as follows. Treatment of 82 with methoxymethylenetriphenylphosphorane afforded two enol-ethers 92 which upon hydrolysis with perchloric acid in ether gave a mixture of at least two diastereomeric products 93. Clemensen reduction of 93 with activated zinc powder in ether saturated with dry hydrogen chloride gave rise to a mixture of compounds from which only one desired product was obtained. The structure

---

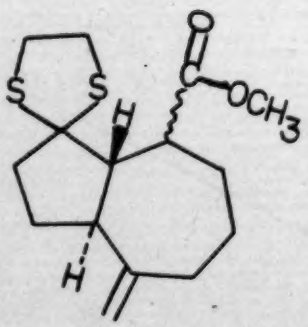
* On the basis of the present work these structural assignments are apparently in error.



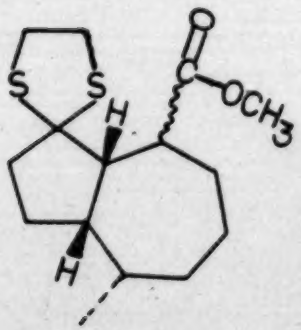
85



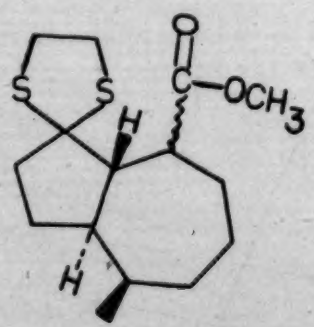
86



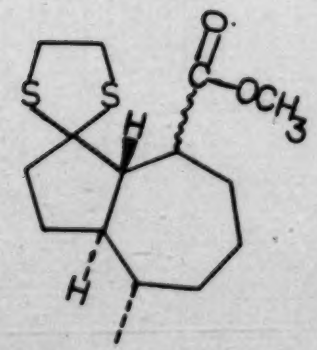
87



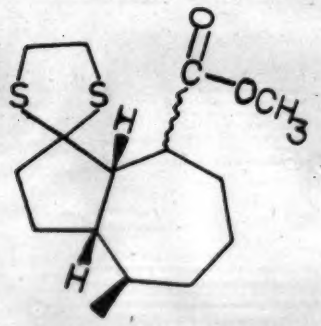
88



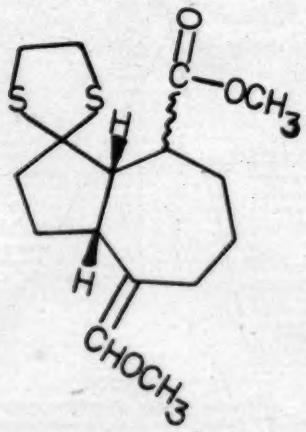
89



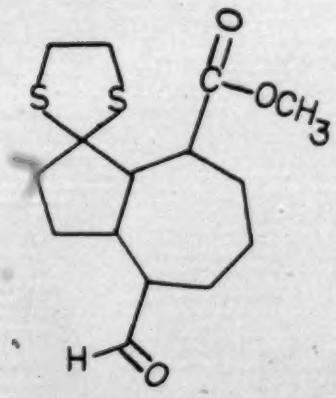
90



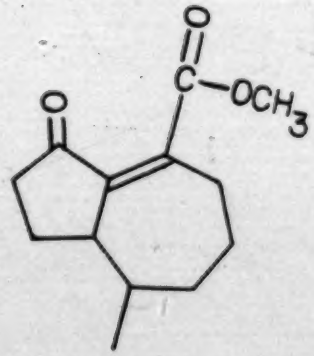
91



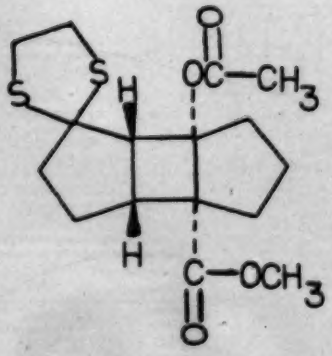
92



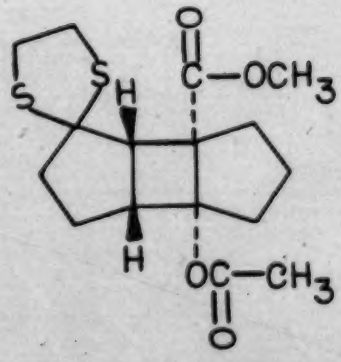
93



94

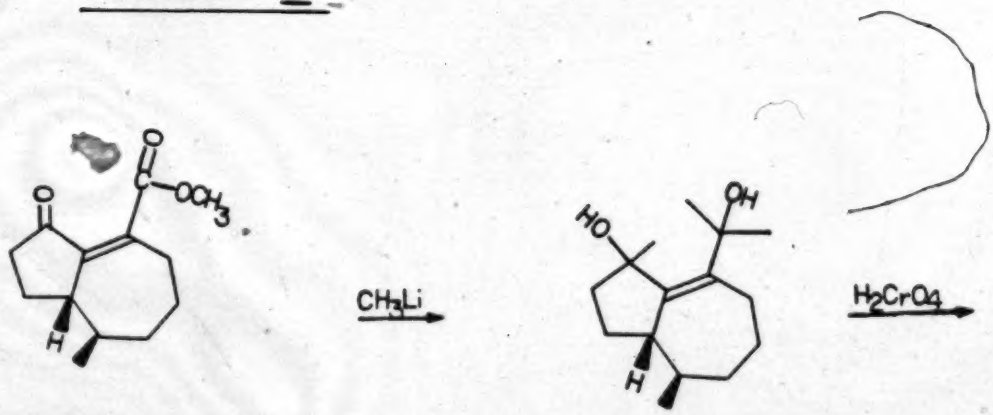


95

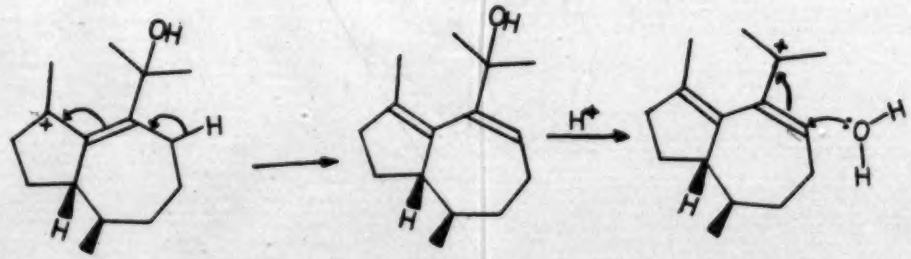


96

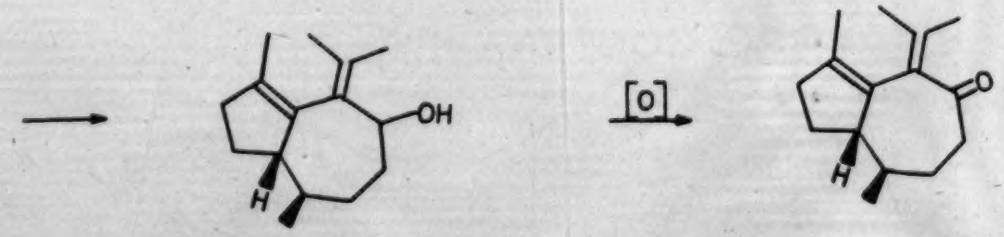
SCHEME I



94 94a



94b 94c 94d

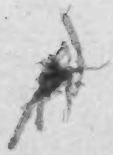


94e I

91 was assigned to this product. Corleto also attempted the conversion of (88→91) to the enone-ester 94 in order to proceed with the synthesis of zierone (1) via the proposed scheme I. Efforts directed towards this end were totally fruitless as compound 94 could not be formed using various methods.

It was recognised at the outset of the present work that the stereochemical assignments (88→91) were made solely from theoretical considerations. As a result of this uncertainty of the stereochemical assignments and the lack of control of the stereochemistry of the C-1 and C-10 centres, as well as the difficulties encountered in the formation of 94, coupled with the fact that one of the objectives of the synthesis of zierone is to confirm its structure and stereochemistry, the above approach was found to be inadequate therefore an alternative approach to the synthesis of zierone (1) became necessary and this is the subject matter of this thesis.

RESULTS AND DISCUSSION

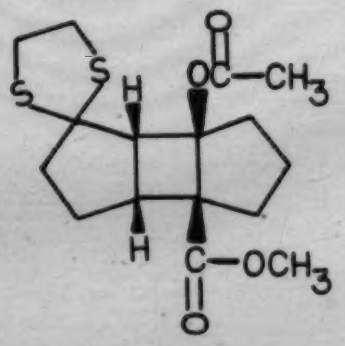


CHAPTER II: PHOTOCYCLOADDITION OF 2-CYCLOPENTENONE AND 1-ACETOXY-2-CARBOMETHOXYCYCLOPENTENE AND STRUCTURAL ELUCIDATION OF ADDUCTS.

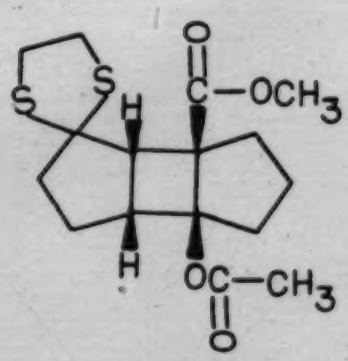
The photocycloaddition reaction was carried out using benzene as the solvent according to the procedure of Corleto.[51] After removal of the solvent, the unreacted starting compound 75 was recovered by distillation and the wide mixture of products was treated with 1,2-ethanedithiol and a catalytic amount of boron trifluoride etherate to form the thioketals of the ketonic adducts. A careful column chromatographic separation of the products on silica gel afforded two oily fractions in a ratio of 1.4:1 and in a total yield of approximately 62% from cyclopentenone. The major fraction which is faster moving on tlc (silica gel) was partially crystallized from n-pentane - diethyl ether to afford a crystalline material which was shown after further investigation to have the structure and stereochemistry assigned to 95. After rechromatography of the mother liquor of 95, a second thioketalized product was obtained. This was shown to possess the structure and stereochemistry assigned to 96. Thus the thioketalized photocycloadduct was found to contain approximately 29% of 95 and 8% of 96. The slower moving fraction (per tlc analysis), which was the minor component of the thioketalized photocycloadducts was also partially crystallized to afford a crystalline compound which was found to possess the structure and stereochemistry assigned to 97. Further chromatography of the mother liquor of 97 afforded the compound which was assigned the structure and stereochemistry of 98. Thus the thioketalized products consisted of approximately 22% of 97 and 3% of 98.

These results indicated that the photocycloadducts consisted of a mixture of all four possible diastereomers 101, 102, 103 and 104 and not three as had earlier been indicated by Corleto.[51] The regioisomer with the gross structure shown in 99 was formed in a total of 51% yield while the regioisomer 100 with the opposite orientation was formed in a total of 11% yield. It was recognised that both isomers could be used as the hydroazulene precursor in the synthetic studies of zierone. However in view of the low yield of 100 when benzene was used as solvent, the photocycloaddition reaction was repeated using methanol as solvent with the objective of improving the overall yield of 100 or its ketone analogue 100a.

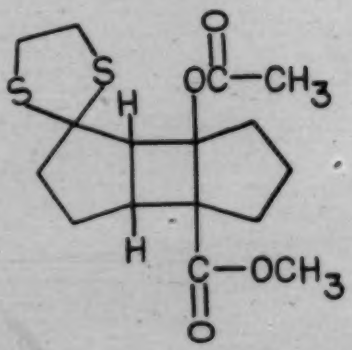
When methanol was used as a solvent in the photocycloaddition reaction a complex mixture of products was obtained. The crude product was purified by column chromatography on silica gel followed by high pressure liquid chromatography separation to afford 101 as the only isolable desired product in 20% yield. The low yield of 101 was possibly due to secondary reactions arising from methanolysis of the initially formed photocycloaddition products. Although the secondary reaction products could not be isolated in the pure form, the infrared and pmr spectra of one of the column chromatography fractions suggested the presence of compounds such as 100c and 100d. It was therefore thought that by using a bulkier alcohol such as 2-propanol as solvent the alcoholysis secondary reaction could be minimized or



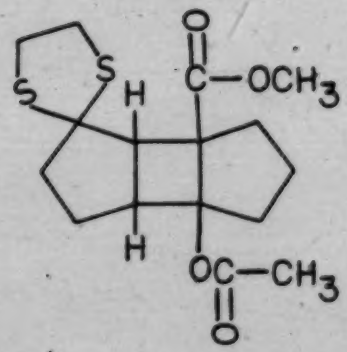
97



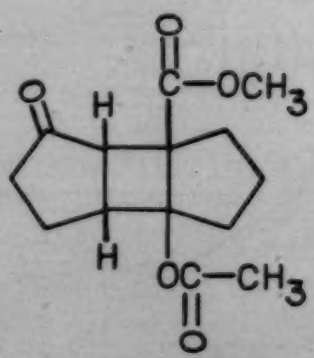
98



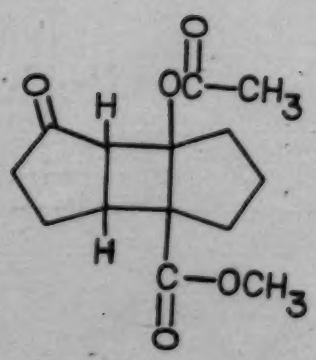
99



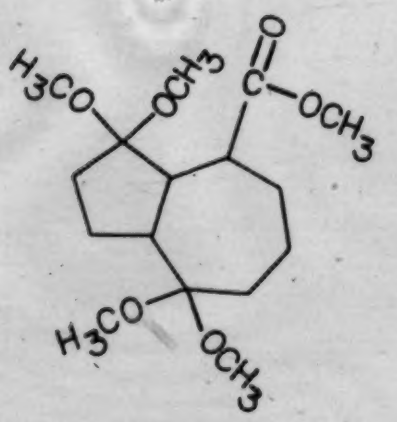
100



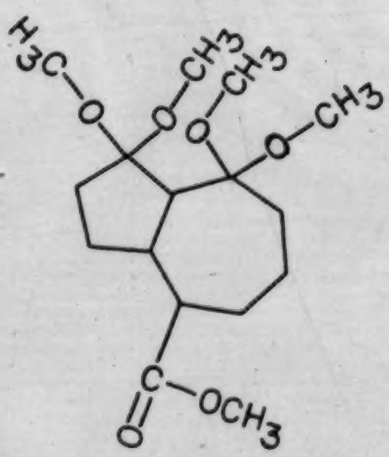
100a



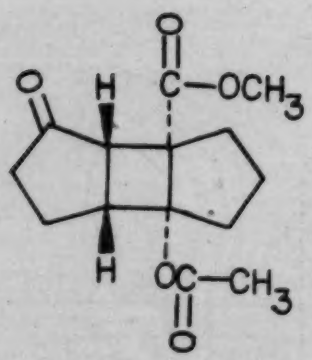
100b



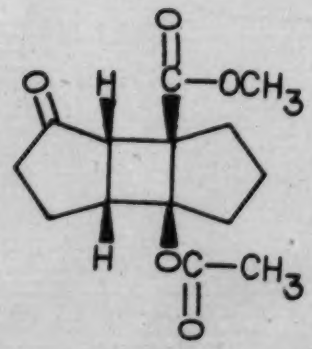
100c



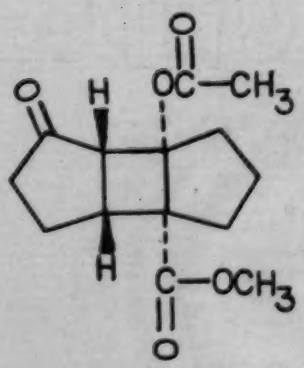
100d



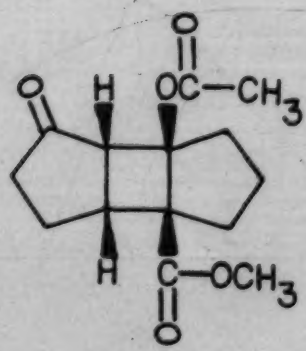
101



102



103

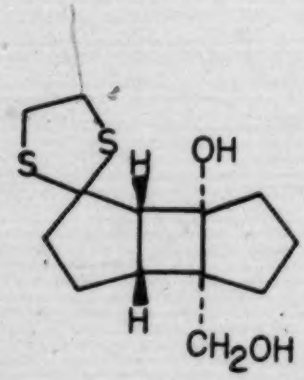


104

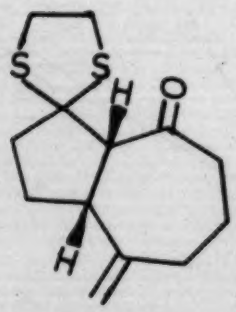
eliminated. Indeed, when the photocycloaddition reaction was carried out in 2-propanol the reaction product was less complex than it was for methanol and there was no evidence of the presence of secondary reaction products. The desired products were separated by repeated column chromatography on silica gel to give 101 in 50% yield and 103 in 10% yield. At this stage it should be pointed out that the structure and stereochemistry assigned to all of the photocycloadducts and their respective thioketals were supported by chemical evidence and not solely by theoretical speculations, and these assignments are discussed as follows.

The infrared spectrum of the pure crystalline compound 95 showed two strong carbonyl absorptions at 1725 cm^{-1} and 1735 cm^{-1} for the two ester functionalities. The pmr spectrum indicated signals at δ 2.1 (s, 3H) for the acetoxy methyl protons, δ 3.62 (s, 3H) for the carbomethoxy methyl protons and δ 3.2 (m, 4H) for the thioketal methylene protons. A mass spectral analysis showed a molecular ion peak at 342.0952 corresponding to $C_{16}H_{22}O_4S_2$. These spectral data are in good agreement with the assigned structure of 95. Lithium aluminum hydride reduction of 95 afforded only one product 105 in 93% yield. The infrared spectrum of 105 showed a broad hydroxyl bands at 3420 cm^{-1}. The pmr spectrum portrayed resonance absorptions at δ 3.29 (s, 2H) due to the hydroxymethyl (HO-CH_2-) protons and δ 3.25 (m, 4H) due to the thioketal methylene protons. The mass spectrum showed a molecular ion peak at 272.0909 in agreement

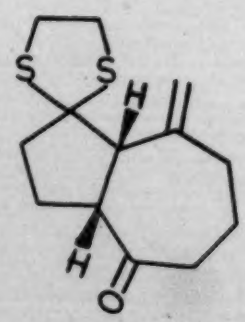
with the required molecular formula, $C_{13}H_{20}O_2S_2$. Confirmation of the orientation of the hydroxymethyl and the tertiary hydroxyl groups relative to the thioketal moiety was obtained after further transformations of 105. Treatment of 105 with p-toluenesulfonyl chloride in pyridine afforded quantitatively the ring cleavage product 106 apparently via the selective formation of the p-toluenesulfonate of the primary alcohol followed by a Grob-type fragmentation involving the tertiary hydroxyl group. Compound 106 which consists of a functionalized hydroazulene skeleton was envisaged as a useful intermediate for the synthesis of zierone, and the feasibility of such a route was investigated. The spectral data of 106 supported the assigned structure. The infrared spectrum showed a strong carbonyl absorption at 1705 cm^{-1} for a cycloheptanone ketone carbonyl and a carbon-carbon double bond absorption at 1680 cm^{-1}. The pmr spectrum portrayed vinylic proton signals at δ 4.77 and δ 4.82 weakly coupled to each other, ($J < 0.5$ Hz). It also showed resonance signals at δ 3.25 (m, 4H) for the thioketal methylene protons and δ 3.16 (d, 1H, $J = 9$ Hz) attributed to the C-5 proton which is cis and coupled to the C-1 proton. The cis stereochemistry is assigned due to the mild conditions employed in the fragmentation of 105 to give 106 since only one product was obtained and the complete epimerization of the C-5 centre is unlikely to occur under the reaction conditions. The cis stereochemistry is also supported by the low value of the coupling constant. The



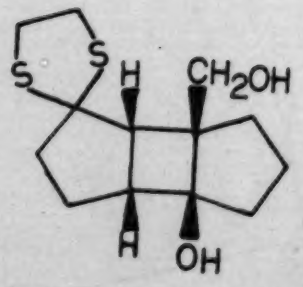
105



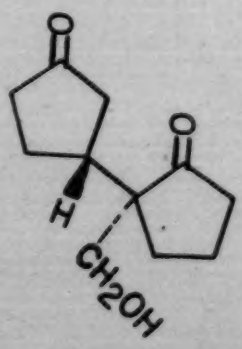
106



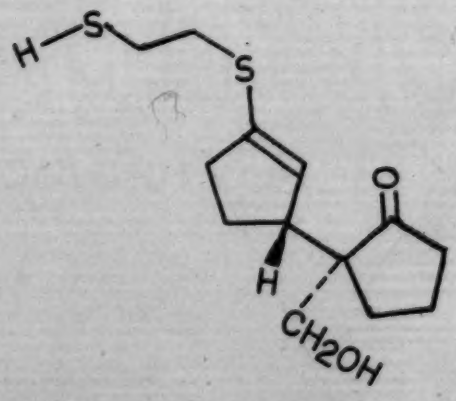
107



108



109



110

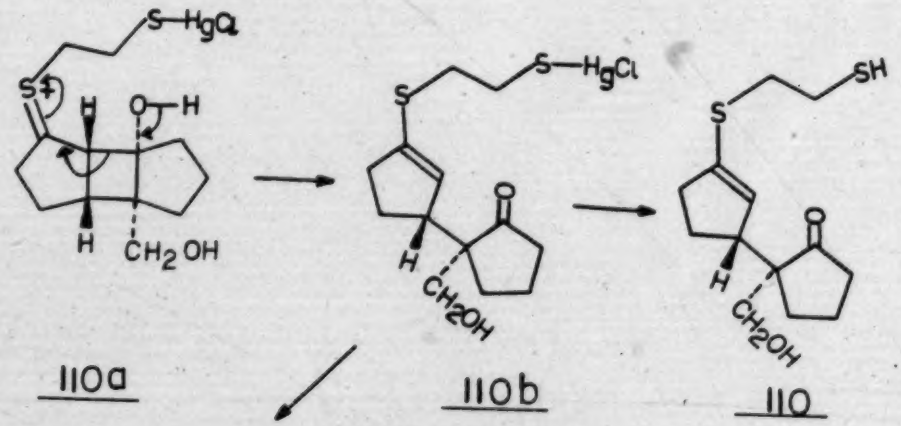
mass spectrum also gave a molecular ion peak at 254.0801 in agreement with the molecular formula of $C_{13}H_{18}OS_2$. Although the spectral data obtained for 106 could equally well be explained by the structure of 107 arising from the diol 108, further evidence was obtained for the assigned structures of 105 and 106 by hydrolysis of 105. Thus upon treatment of 105 with mercuric chloride in aqueous acetonitrile the expected dihydroxy-ketone was not formed, instead, three products were obtained which were identified as 109, 110 and 111. The hydroxy diketone 109 showed a broad hydroxyl band at 3450 cm^{-1} and a strong carbonyl absorption at 1740 cm^{-1} for the cyclopentanone ketonic groups in the infrared spectrum. In the pmr spectrum resonance signals were observed at δ 5.85 (br. s, 1H) for the hydroxyl proton and δ 3.6 (s, 2H) for the methylene protons adjacent to the hydroxyl group. The mass spectrum gave the molecular ion peak at 196.1098 in agreement with the molecular formula $C_{11}H_{16}O_3$. The structure of the hydroxy diketone 109 was further confirmed by acetylation with acetic anhydride in pyridine to give the acetate 112. The acetate showed carbonyl absorptions at 1735 cm^{-1} for the acetoxy group and at 1750 cm^{-1} for the cyclopentanone carbonyl groups, with the disappearance of the hydroxyl band of 109 from 3450 cm^{-1}. The pmr absorption signals appeared at δ 4.15 (s, 2H) for the methylene protons of the acetoxymethyl moiety and at δ 2.1 (s, 3H) for the methyl protons of the acetoxy group. The infrared spectrum of 110 showed a broad hydroxyl band

at 3450 cm^{-1} and a carbonyl absorption band at 1745 cm^{-1} for the cyclopentanone ketone group. The pmr spectrum portrayed resonance signals at δ 5.2 (m, 1H) for the vinylic proton and at δ 3.7 (s, 2H) for the methylene protons adjacent to the hydroxyl group. The acetylated derivative of 110 was also prepared and identified as 113. Its pmr spectrum showed resonance signals at δ 2.05 (s, 3H) due to the acetoxy methyl protons, δ 2.35 (s, 3H) due to the thiol ester methyl protons, δ 4.15 (d, 2H, J = 2 Hz) for the methylene protons of the acetoxymethyl moiety, δ 5.5 (m, 1H) for the vinylic proton weakly coupled to the allylic protons and at δ 3.0-3.2 (m, 4H) due to the methylene protons of the $-S-CH_2-CH_2-S-$ system. The infrared spectrum of the diketo-ether 111 showed two carbonyl absorptions at 1740 cm^{-1} and 1750 cm^{-1} for the two cyclopentanone ketone carbonyl groups. Its pmr spectrum showed signals at δ 4.38 (d, 1H, J = 6 Hz) assigned to the proton of the methine group bearing the oxygen atom, δ 3.65; 3.69 (1H each, both d, J = 14 Hz each) due to the geminally coupled methylene protons of the tetrahydrofuran ring and at δ 3.05 (dd, 1H, J = 7 Hz, J' = 6 Hz) for the methine proton beta to both carbonyl groups. The molecular weight of 194.1969 corresponding to $C_{11}H_{14}O_3$ is supported by its observation in the mass spectrum. Although the formation of 109, 110 and 111 from 105 was unexpected, the isolation of these products provided further evidence for the assigned orientation of the hydroxymethyl and the tertiary hydroxyl groups relative to the thioketal

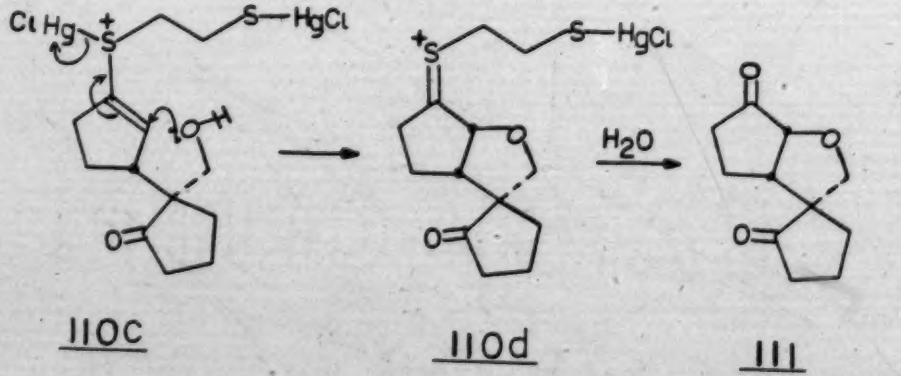
moiety of 105. The formation of these compounds can be explained by invoking the intermediacy of the sulfonium complex 110a as shown in scheme II. A Grob-type cleavage of the cyclobutane ring of 110a would give 110b which would give 110 on protonation. However interception of 110b by mercuric chloride would give 110c which could undergo a Michael-type addition of the hydroxyl group to give the sulfonium complex 110d. Hydrolysis of 110d would then give 111. Finally, hydrolysis of the sulfonium complex 110a would give the dihydroxy-ketone 110e which could undergo a retro-aldol type fragmentation to afford 109. These results clearly established the gross structure of 95, however further evidence was obtained to support the structure and to establish the stereochemistry of 95 and these will be discussed at the appropriate stage.

The structure of 96 was also established through similar chemical transformations. Reduction of 96 with lithium aluminum hydride afforded two products identified as 114 and 115. The infrared spectrum of 114 showed a broad hydroxyl band at 3500 cm^{-1}. The pmr spectrum portrayed signals at δ 3.25 (m, 4H) indicative of the methylene protons of the thioketal moiety and at δ 3.9 as a broad weakly coupled doublet for the methylene protons of the hydroxymethyl moiety. The mass spectral analysis of 114 agreed with the assigned molecular formula of $C_{13}H_{20}O_2S_2$ with a molecular weight of 272.0909 as observed. The infrared spectrum of 115 showed a broad hydroxyl band at 3400 cm^{-1} for the

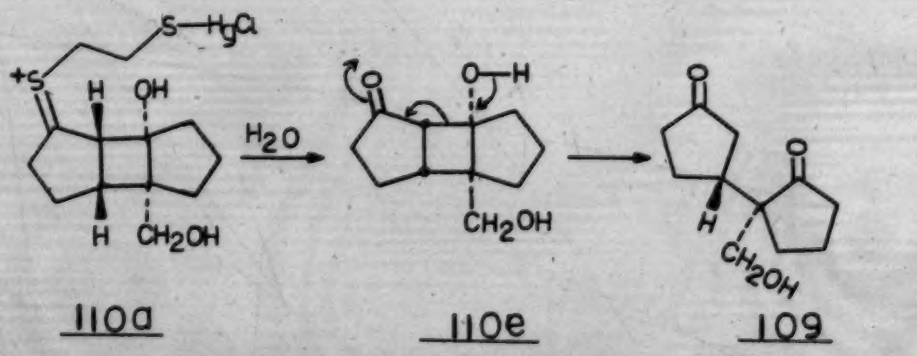
SCHEME II



110a 110b 110



110c 110d 111



110a 110e 109

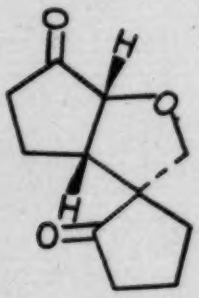
tertiary hydroxyl group. The pmr spectrum portrayed resonance signals at δ 4.2-4.5 (m, 2H) for the C-1 proton and the hydroxyl proton and a characteristic AB system at δ 3.5 (d, 1H, J = 12 Hz) and δ 4.2 (d, 1H, J = 12 Hz) attributed to the methylene protons of the tetrahydrofuran ring. The mass spectrum collaborated the assigned structure with a molecular ion peak at 180.1148 corresponding to $C_{11}H_{16}O_2$. When 114 was treated with p-toluenesulfonyl chloride in pyridine it gave 116 as the only product. The mass spectrum of 116 gave a molecular ion peak at 254.0801 for $C_{13}H_{18}OS_2$. The infrared spectrum showed a broad hydroxyl band at 3500 cm^{-1} and a weak band at 1690 cm^{-1} attributed to the carbon-carbon double bond. The pmr spectrum showed a weakly coupled triplet at δ 5.9 (1H) attributed to the vinylic proton and signals at δ 3.28 (t, 2H, J = 3 Hz) for the methylene protons (=$\overset{1}{C}$-S-$\underline{CH_2}$-), δ 2.6-3.0 (m, 4H) for the protons of the methylene groups directly attached to the sulfur atom (-$\underline{CH_2}$-S-$\underline{CH_2}$-). The formation of 114 and 115 as well as the conversion of 114 into 116, coupled with the fact that no similar cyclic products were obtained in the reduction of 95 which gave exclusively 105, led to the assignment of the structure and stereochemistry of 96 as shown. Detailed discussion of the stereochemical consequences of these reactions leading to the assigned structures and stereochemistry will be given later when further evidence for the confirmation of these structures becomes available and when the analysis of the other thioketalized

photocycloadducts 97 and 98 is completed.

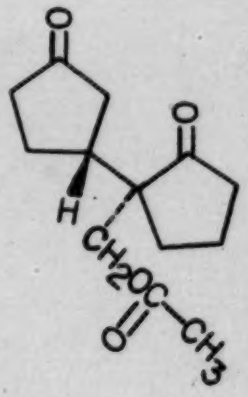
The minor component of the thioketalized product of the photocycloaddition reaction, the slower moving fraction per tlc analysis, was also analysed and shown to consist of 97 and 98. The infrared spectrum of compound 98 showed two carbonyl absorptions at 1735 and 1745 cm^{-1} for the two ester groups. The pmr spectrum portrayed signals at δ 1.98 (s, 3H) for the acetoxy methyl protons, δ 3.35 (m, 4H) for the m methylene protons of the thioketal moiety and δ 3.7 for the carbomethoxy methyl protons. The mass spectrum gave a molecular ion peak at 342.0952 corresponding to $C_{16}H_{22}O_4S_2$. Reduction of 98 afforded the diol 108. The infrared spectrum of 108 showed a broad hydroxyl band at 3400 cm^{-1} for both the primary and tertiary hydroxy groups, while its pmr spectrum showed signals at δ 3.68 (s, 2H) for the methylene protons of the hydroxymethyl group and δ 3.3 (m, 4H) due to the methylene protons of the thioketal moiety. The mass spectrum gave a molecular ion peak at 272.0909 corresponding to $C_{13}H_{20}O_2S_2$. Treatment of 108 with p-toluenesulfonyl chloride in pyridine resulted in the formation of a gummy material from which no identificable product could be isolated. However further evidence for the correctness of structure 98 would be provided at the appropriate stage.

The photocycloadduct 97 showed two carbonyl abosorptions at 1735 and 1745 cm^{-1} for the two ester groups in its infrared spectrum. The pmr displayed signals at δ 1.98 (s, 3H) for the acetoxy methyl protons, δ 3.70 (s, 3H) for the

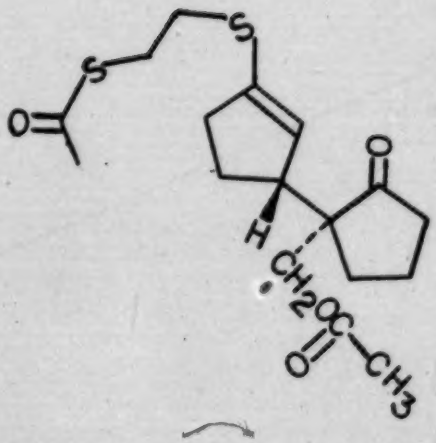
carbomethoxy methyl protons and at δ 3.35 (m, 4H) for the methylene protons of the thioketal moiety. The mass spectrum also gave a molecular ion peak at 342.0952 corresponding to $C_{16}H_{22}O_4S_2$. Reduction of 97 with lithium aluminum hydride afforded only one product 117 in quantitative yield. The infrared spectrum of the diol 117 showed a strong hydroxyl band at 3400 cm^{-1} for both the primary and tertiary hydroxyl groups. Its pmr spectrum displayed resonance signals at δ 3.70 (s, 2H) for the methylene protons of the hydroxymethyl group, δ 3.2-3.4 (m, 4H) for the thioketal methylene protons and at δ 0.9-3.1 for the hydroxyl and the carbocyclic protons. The mass spectrum gave a molecular ion peak at 272.0909 in agreement with the expected molecular formula of $C_{13}H_{20}O_2S_2$. Further evidence for the assignment of structure 117 was obtained when 117 was treated with p-toluenesulfonyl chloride in pyridine to afford 118 via the formation of the p-toluensulfonate of the primary alcohol. The infrared spectrum of 118 portrayed a strong carbonyl absorption at 1705 cm^{-1} which is attributed to the cycloheptanone carbonyl group and a medium absorption band at 1680 cm^{-1} due to the exocyclic carbon-carbon double bond. The pmr spectrum showed two resonance signals at δ 4.77 (d, 1H, $J < 0.5$ Hz) and δ 4.82 (d, 1H, $J < 0.5$ Hz) for the vinylic protons, δ 3.25 (m, 4H) for the thioketal methylene protons, and at δ 3.16 (d, 1H, $J = 9$ Hz) which is assigned to the C-5 proton, cis and coupled to the allylic proton at C-1. The mass spectrum gave a molecular ion peak at



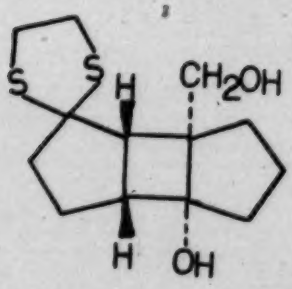
111



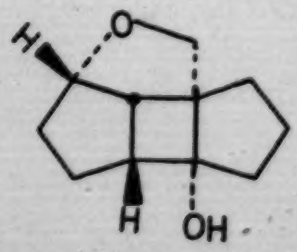
112



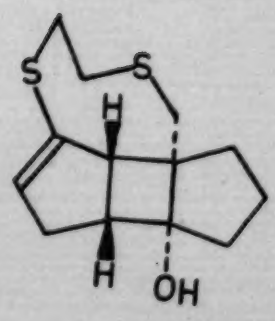
113



114



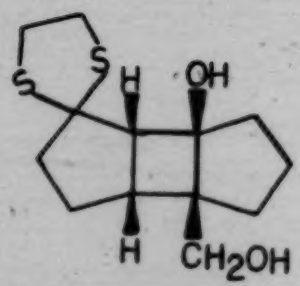
115



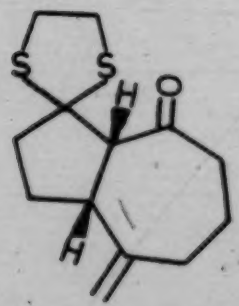
116

254.0801 corresponding to $C_{13}H_{18}OS_2$. The spectral data are clearly in agreement with the assigned structure and in fact showed that 118 and 106 are identical. Both compounds were also found to have the same melting point (64-65°C) and the same R_f value by thin layer chromatography comparison. The fact that 118 and 106 were identical clearly proved that their precursors 97 and 95 respectively were different from each other only in the stereochemistry of the fused ring junction containing the acetoxy and the carbomethoxy moieties. A final proof for the gross structures of 95 and 97 was obtained when 106 and 118 were separately treated with sodium hydride and methyl iodide to give the same compound 119 in 87% yield each. The infrared spectrum of 119 showed a carbonyl absorption at 1645 cm^{-1} and a carbon-carbon double bond absorption at 1525 cm^{-1}. These are in support of the α,β-unsaturated seven-membered ring ketone system. In the pmr spectrum resonance signals appeared at δ 4.85 (s, 2H) for the exocyclic vinylic protons, δ 3.7 (t, 1H, J = 8 Hz) for the allylic methine proton, δ 2.19 (s, 3H) for the methyl protons of the methyl group directly attached to sulfur. The mass spectrum gave a molecular ion peak at 268.0958 which is in agreement with the assigned molecular formula of $C_{14}H_{20}OS_2$. Since 107 cannot be transformed into 119 under the reaction conditions it can be concluded that the structural assignments made for all of the precursors of 119 are in fact correct.

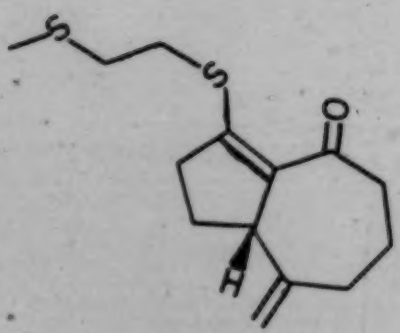
So far the chemical transformations of the thioketalized



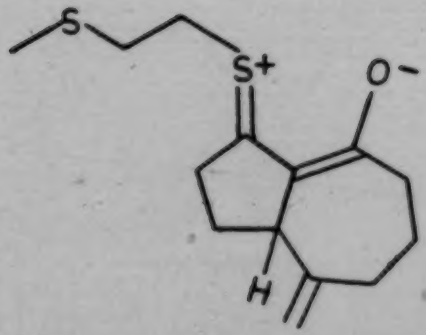
117



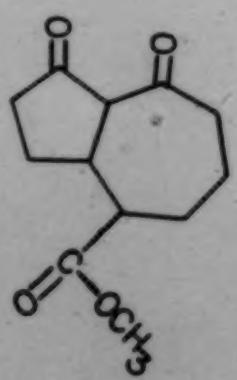
118



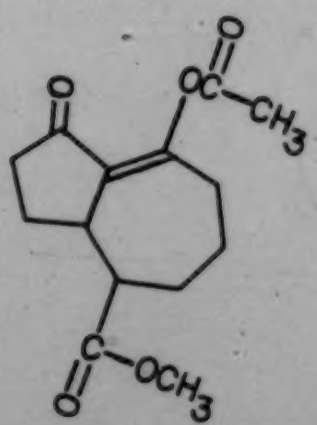
119



119a



120



121

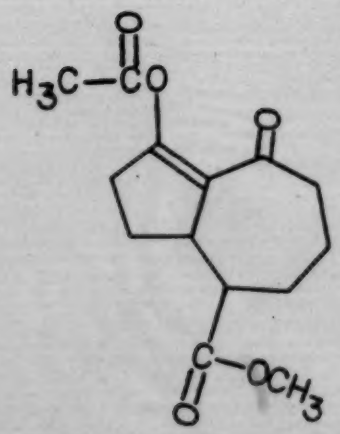
photocycloadducts have provided information for the assignment of the gross structures of the compounds involved in these transformations. From these results it can be concluded that there are two pairs of regioisomers with respect to the orientation of the acetoxy and the carbomethoxy moieties relative to the thioketal group. The diastereomers 95 and 97 which constitute one pair of regioisomers have the same gross structure but differ in the stereochemistry at the ring junction containing the acetoxy and the carbomethoxy moieties. The diastereomers 98 and 96 which constitute the other pair of regioisomers also have the same gross structure but differ in the stereochemistry of the acetoxy and the carbomethoxy ring junction.

In order to assign the stereochemistry of these compounds further reactions were carried out on their respective ketone analogues. During the course of this stereochemical elucidation further evidence was obtained which also supported the assigned structures. In this connection, the thioketals were hydrolysed to give back the original ketones produced in the photocycloaddition reaction. Thus the crystalline thioketal 97 was treated with mercuric chloride in aqueous acetonitrile to afford only one product 104 in 95% yield. It gave a molecular weight of 266.1117 in its mass spectrum, corresponding to $C_{14}H_{18}O_5$. This compound showed three carbonyl absorptions in the infrared spectrum at 1725 cm^{-1} and 1735 cm^{-1} due to the two ester groups and also at 1750 cm^{-1} due to the cyclopentanone

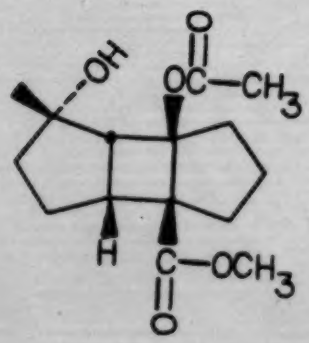
keto-carbonyl group. The pmr spectral analysis portrayed significantly signals at δ 2.1 (s, 3H) for the acetoxy methyl protons and at δ 3.71 (s, 3H) for the carbomethoxy methyl protons. These features agree with the assigned structure. Furthermore when 104 was treated with sodium hydroxide in aqueous methanol it produced a diketone 120, the structure of which was confirmed by acetylation with acetic anhydride in pyridine to give 121 in 95% yield and 122 in approximately 5% yield. The infrared spectrum of 120 showed strong absorptions at 1735 cm^{-1} for the ester carbonyl group and also at 1705 cm^{-1} and 1620 cm^{-1} for the β-hydroxy-enone system expected for 120. The rather low carbonyl absorption frequency compared to the normal absorption frequency of cyclopentenone ketones suggested a β-diketone functionality. This spectral data coupled with the ease of acetylation confirmed the presence of a β-diketone system. The pmr spectrum of 120 showed a signal at δ 3.68, (s, 3H) for the methyl protons of the carbomethoxy group, in addition to the signals of the carbocyclic ring protons which appeared as a multiplet at δ 1.2-2.3. The mass spectrum also showed a molecular ion peak at 224.1046 for $C_{12}H_{16}O_4$ in support of the structure. The major acetylation product which constituted 95% of the product mixture showed intense absorptions at 1640 cm^{-1} for the carbon-carbon double bond, 1735 cm^{-1} for the carbomethoxy carbonyl group, 1720 cm^{-1} for the cyclopentenone carbonyl group and at 1765 cm^{-1} for the acetoxy carbonyl group of the enol

acetate. The pmr spectrum further confirmed the structure as it showed signals at δ 2.2 (s, 3H) for the acetoxy methyl protons and at δ 3.68 (s, 3H) for the carbomethoxy methyl protons.

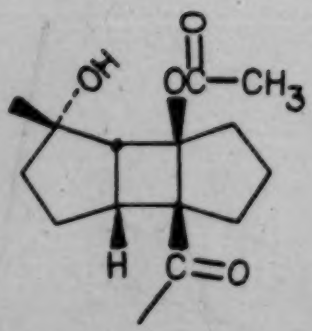
The keto-diester 104 was treated with methyl lithium in dry diethyl ether at -78°C for two hours and the cold reaction mixture was poured into saturated aqueous ammonium chloride solution and extracted with diethyl ether. After isolation of products and separation by column chromatography on silica gel, three products identified as 123, 124 and 125 in a ratio of 7:1:1 respectively and in a total yield of 90% were obtained. The remaining 10% was isolated as unreacted starting material. The structures assigned to these compounds were in agreement with their spectral data. The infrared spectrum of 123 showed a broad hydroxyl band at 3500 cm^{-1} for the tertiary hydroxyl group and a very intense carbonyl absorption at 1725 cm^{-1} due to the two ester groups. The pmr spectrum displayed signals at δ 4.15 (s, 1H) assigned to the hydroxyl proton, δ 3.75 (s, 3H) for the carbomethoxy methyl protons, δ 2.55 (d, 1H, J = 9 Hz) for the proton beta to both the acetoxy and hydroxy groups, and cis to the C-1 proton to which it is coupled, δ 1.96 (s, 3H) for the acetoxy methyl protons and δ 1.18 (s, 3H) due to the protons of the methyl group introduced by the reaction with methyl lithium. The formation of 124 was due to further reaction of 123 with methyl lithium at the carbomethoxy carbonyl, while 125 arose by further reaction of 123 with



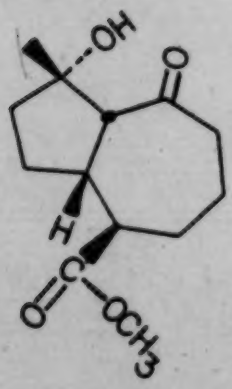
122



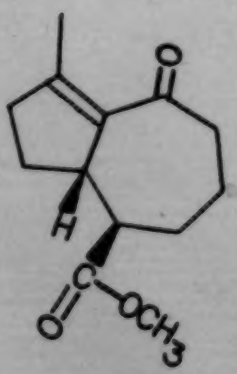
123



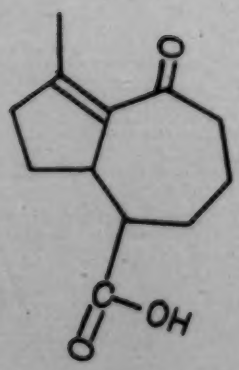
124



125



126



127

methyl lithium at the acetoxy carbonyl with subsequent ring opening of the cylcobutane ring. The infrared spectrum of 125 showed the presence of a hydroxyl group absorption at 3500 cm^{-1} and two carbonyl absorptions at 1710 cm^{-1} for the saturated seven-membered ring ketone and at 1725 cm^{-1} for the ester functionality. Upon treatment with sodium methoxide in methanol 125 afforded 126 quantitatively. The spectral data of 124 are also in agreement with the assigned structure. The infrared spectrum showed a broad hydroxyl band at 3500 cm^{-1} and two carbonyl absorptions for the methyl ketone and ester functionalities at 1710 cm^{-1} and 1725 cm^{-1} respectively. There were notably three resonance peaks in the pmr spectrum at δ 2.26 (s, 3H) for the methyl protons of the methyl ketone, δ 2.02 (s, 3H) for the acetoxy methyl protons and at δ 1.24 (s, 3H) for the C-3 methyl protons. The hydroazulene ring skeleton was obtained by hydrolysis of the acetoxy group of 123 with aqueous sodium hydroxide in methanol with accompanying elimination of water to give 126, isolated from the basic reaction mixture and 127, isolated after acidification of the reaction mixture in an approximate ratio of 3:1. The infrared spectrum of 126 consisted of three strong absorptions, at 1735 cm^{-1} for the ester carbonyl, 1675 cm^{-1} due to the α,β-unsaturated ketone of the seven-membered ring and at 1615 cm^{-1} due to the carbon-carbon double bond. The pmr spectrum portrayed resonance peaks at δ 3.65 (s, 3H) for the carbomethoxy methyl protons and at δ 2.1 (s, 3H) for the vinylic methyl

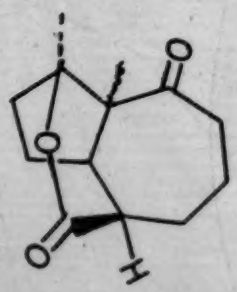
protons. The mass spectrum also gave a molecular ion peak of 222.1263 for $C_{13}H_{18}O_3$. These spectral data support the structure of 126, hence confirming the structures of the precursors of 126. The stereochemistry assigned to 126 was also proved to be correct (vide infra). An attempt was made to methylate the acid 127 with methyl iodide in acetone in the presence of potassium carbonate, however only 10% of the desired product 126, was obtained, the major product being the δ-lactone 128. Its infrared spectrum showed a saturated seven-membered ring ketone absorption at 1700 cm^{-1} and a δ-lactone carbonyl absorption at 1740 cm^{-1}. Its pmr spectrum also showed the presence of two methyl groups at δ 2.22 (s, 3H) for the ring junction methyl protons and at δ 1.35 (s, 3H) for the C-2 methyl protons. The mass spectrum gave a molecular weight of 222.1263 for $C_{13}H_{18}O_3$.

It can clearly be seen that 126 could serve as a useful intermediate compound for the synthesis of zierone, the target molecule, as the ester functionality can be converted into the C-10 methyl group, and the ketone group can be manipulated for the introduction of the isopropylidene and the C-7 ketone groups in zierone, 1. It is also useful, in that, the double bond in the five-membered ring would have been introduced regio stereoselectively in the desired position in the early stages of the synthesis.

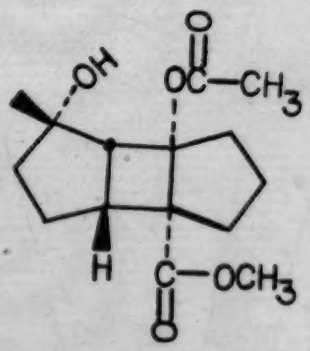
It has already been shown that 97 and 95 differ only in the stereochemistry of the ring junction containing the acetoxy and carbomethoxy moieties. It was therefore

expected that 95 could also afford 126. The thioketal moiety of 95 was therefore hydrolysed with mercuric chloride in aqueous acetonitrile to give the ketone 103. The infrared spectrum of 103 showed absorption bands at 1750 cm^{-1} corresponding to the cyclopentanone carbonyl group, 1720 cm^{-1} and 1730 cm^{-1} for the two ester groups. The pmr spectrum showed resonance signals at δ 1.98 (s, 3H) for the acetoxy methyl protons and at δ 3.66 (s, 3H) for the carbomethoxy methyl protons. The mass spectrum gave a molecular ion peak at 266.1117 for $C_{14}H_{18}O_5$. When 103 was treated with sodium hydroxide in aqueous methanol it produced a diketone identical with 120. Upon acetylation, with acetic anhydride in pyridine 120 afforded the acetylated compounds identical with 121 and 122. These results again showed that 95 and 97 differed in the stereochemistry of the ring junction containing the acetoxy and the carbomethoxy moieties.

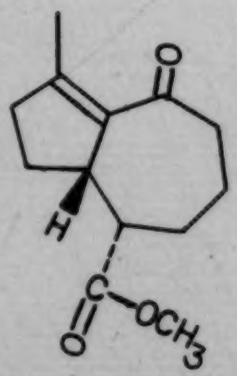
When 103 was treated with methyllithium in diethyl ether at -78°C and the reaction mixture poured into saturated aqueous ammonium chloride solution and extracted with diethyl ether, three products were isolated after separation by column chromatography. These were identified as 126, 130 and 133, in addition to a fourth fraction enriched in 129. The keto-esters 126 and 130 together constituted approximately 50% of the product mixture and 133 constituted about 25%. The spectra of 126 obtained from 103 [ir : 1735 cm^{-1}, 1675 cm^{-1} and 1615 cm^{-1}; pmr δ 3.65 (s, 3H), 2.1 (s, 3H); ms. 222.1263 for $C_{13}H_{18}O_3$] parallel those of 126



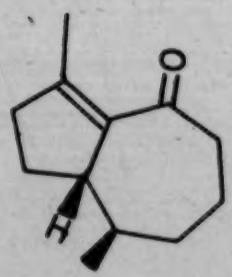
128



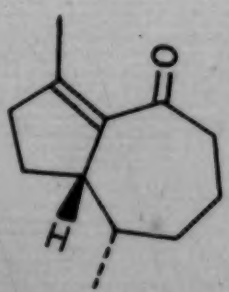
129



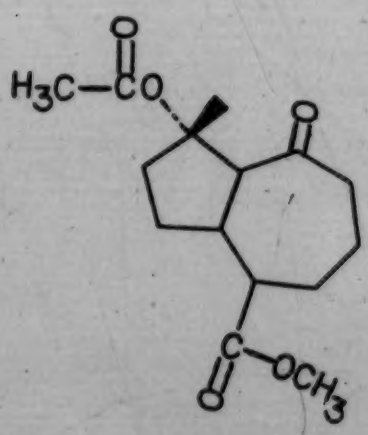
130



131



132



133

previously obtained from 104. Furthermore 126 obtained from both precursors 103 and 104 were independently converted into the same known compound 131.[31] (vide infra) The infrard spectrum of 130 showed carbonyl absorptions at 1730 cm^{-1} for the ester group and at 1670 cm^{-1} for the α,β-unsaturated seven-membered ring ketone carbonyl group and a carbon-carbon double bond absorption at 1610 cm^{-1}. The pmr spectrum showed two prominent signals at δ 2.10 (s, 3H) for the vinylic methyl protons and at δ 3.60 (s, 3H) for the carbomethoxy methyl protons. The mass spectrum gave a molecular ion peak at 222.1263 corresponding to $C_{13}H_{18}O_3$. The infrared spectrum of 133 showed carbonyl absorptions at 1700 cm^{-1} for the saturated seven-membered ring ketone and a much more intense absorption at 1735 cm^{-1} for the two ester carbonyl functionalities. The pmr spectrum displayed signals indicating the presence of two isomers. Resonance signals were observed at δ 1.35 (s, 3H), δ 1.5 (s, 3H) for the C-4 methyl protons, δ 2.05 (s, 3H), δ 2.0 (s, 3H) for the acetoxy methyl protons and at δ 3.7 (s, 3H), δ 3.68 (s, 3H) for the carbomethoxy methyl protons. Upon treatment with methanolic sodium methoxide 133 gave expectedly 126 and 130.

It is interesting to note that while 123 obtained from 104 could be purified by column chromatography on silica gel without any isomerization - with concomitant fragmentation of the four membered ring, an attempt at purification of 129 by column chromatography on silica gel was unsuccessful due

to its substantial conversion into 126, 130 and 133. It is also worth noting that no product isomeric or identical with 125 was produced in the reaction of 103 with methyllithium. This result supports the assertion that 125 was a secondary reaction product of 123 with methyllithium and not a product of transesterification followed by hydrolysis of the resulting acetoxy group. If that were the case 133 would have been capable of producing a compound identical with 125. It should also be noted that no product identical with 126, 130 or 133 was directly formed in the reaction of 104 with methyllithium. These results indeed proved the assigned stereochemistry of the keto-diesters 103 and 104 and consequently the stereochemistry of their respective thioketals 95 and 97. The stereochemistry assigned to 103 and 104 and consequently their precursors was based on the isolation of 123 as the major methyllithium reaction product of 104, coupled with the isolation of 126, 130 and 133 from the reaction of 103 with methyllithium. It was reasoned that as the four membered ring in the photocycloadduct 104 is essentially flat, and therefore the two cyclopentane rings are cis and almost parallel to each other, the methyl carbanion will preferentially approach the ketone carbonyl group from the less hindered side, the side syn to the acetoxy group, consequently the incipient alkoxide would be trans or anti to the acetoxy group and cannot in any way undergo an intramolecular transesterification involving the acetoxy group thereby resulting in a concurrent cleavage of

the cyclobutane ring to form the hydroazulene skeleton. On the other hand reaction of the ketone carbonyl of 103 with methyllithium would result in the formation of an alkoxide syn and close to the acetoxy group and intramolecular transesterification involving the acetoxy group with concurrent cleavage of the four-membered ring to form the hydroazulene skeleton is possible. This reaction is expected to be facile as a result of the release of the ring strain of the rigid cyclobutane ring.

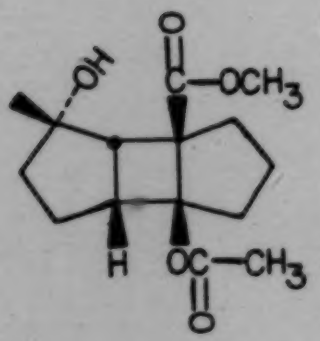
In the light of the foregoing results, it was thought that further chemical transformations of the diastereomers 98 and 96 would lead to the assignment of their stereochemistry. It should be recalled that, from the results obtained earlier in the reduction of 96 with lithium aluminum hydride to give 114 and 115 and the formation of 116 from 114 upon treatment of 114 with p-toluenesulfonyl chloride in pyridine the structure and stereochemistry of 96 was assigned as shown. This assignment was further proven by chemical transformations of 101 obtained from 96 by hydrolysis of the thioketal group with mercuric chloride in aqueous acetonitrile. The hydrolysis product 101 was analyzed to ascertain its composition. Its infrared spectrum showed carbonyl absorptions at 1750 cm^{-1} for the cyclopentanone ketone group, 1730 cm^{-1} and 1735 cm^{-1} for the carbomethoxy and acetoxy carbonyl groups. The pmr spectrum showed resonance signals at δ 2.02 (s, 3H) for the acetoxy methyl protons and at δ 3.65 (s, 3H) for the carbomethoxy

methyl protons. The mass spectrum gave a molecular ion peak at 266.1117 corresponding to the molecular formula $C_{14}H_{18}O_5$. Upon treatment with methyllithium in diethyl ether at -78°C followed by aqueous work up as usual 101 gave 135 as the only product in 85% yield. The infrared spectrum of 135 indicated the presence of a γ-lactone and an ester functionality with absorptions at 1750 cm^{-1} and 1730 cm^{-1} respectively. Its pmr spectrum showed resonance signals at δ 2.02 (s, 3H) for the acetoxy methyl protons, δ 1.5 (s, 3H) for the C-1 methyl protons and at δ 2.3 (d, 1H, J = 9 Hz) for the methine proton on the side of the molecule containing the lactone functionality. The mass spectrum gave a molecular ion peak at 250.1206 for the expected molecular formula, $C_{14}H_{18}O_4$.

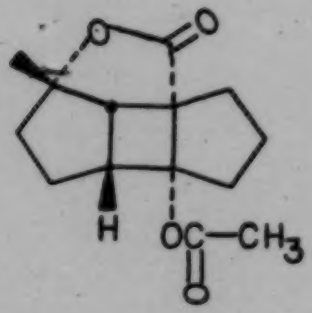
When 135 obtained from 101 was treated with methanolic sodium methoxide it produced an isomeric mixture of 136 and 137. The structure and stereochemistry of which are established later (vide infra). Upon treatment with mercuric chloride in aqueous acetonitrile 98 afforded the keto-diester 102. The infrared spectrum of 102 showed carbonyl absorptions at 1750 cm^{-1} for the cyclopentanone ketone carbonyl group, 1725 cm^{-1} and 1735 cm^{-1} for the two ester functionalities. Its pmr spectrum displayed signals at δ 2.1 (s, 3H) for the acetoxy methyl protons and at δ 3.75 (s, 3H) for the carbomethoxy methyl protons. The mass spectrum of 102 gave a molecular ion peak at 266.1117 corresponding to the expected molecular formula of $C_{14}H_{18}O_5$.

When 102 was treated with methyllithium at -78°C it afforded 134 as the only product in 90% yield. The infrared spectrum of 134 showed a broad hydroxyl band at 3500 cm^{-1} and absorptions at 1725 cm^{-1} and 1730 cm^{-1} due to the two ester functionalities. Its pmr spectrum displayed resonance signals at δ 5.15 (s, 1H) for the hydroxyl proton, δ 3.64 (s, 3H) for the carbomethoxy methyl protons, δ 1.92 (s, 3H) for the acetoxy methyl protons and at δ 1.15 (s, 3H) for the C-3 methyl protons. Upon treatment of 134 with methanolic sodium methoxide two keto-lactones identical with 136 and 137 were formed. The formation of 136 and 137 from both 134 and 135 led to the conclusion that the precursors 102 and 101 differed in the stereochemistry at the ring junction containing the carbomethoxy and the acetoxy moieties. These results also led to the assignment of the stereochemistry of 102 and 101 as shown.

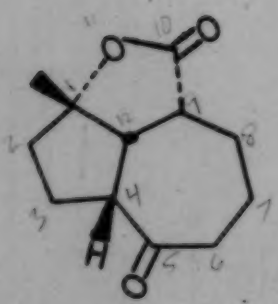
It was reasoned, as before, that the cyclobutane ring in the photocycloadducts is essentially flat. This implies that the cyclopentane ring containing the ketone functionality is cis and almost parallel to the carbomethoxy group in 101. The stereochemical consequence of the reaction with methyllithium is that the methyllithium will attack the ketone carbonyl from the sterically less hindered side. This will produce an incipient alkoxide cis and close to the carbomethoxy group. It is only in such a situation that an intramolecular lactonization involving the alkoxide and the carbomethoxy group can occur, as would be predicted by



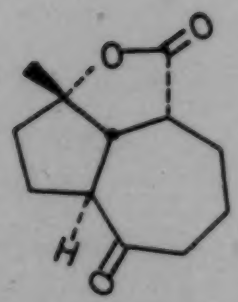
134



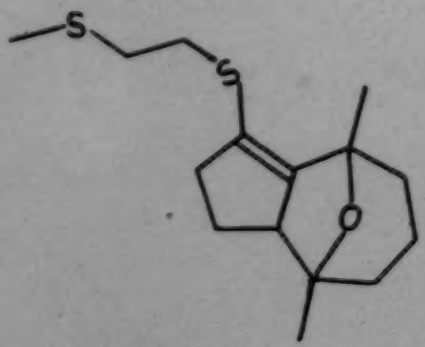
135



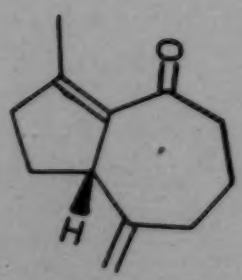
136



137



138



139

the Alder-Stein rule for the formation of lactones[53] which states that "In alicyclic γ-hydroxy acids, lactones can only form if the groups are cis." On the other hand, the alkoxide produced by the reaction of 102 with methyllithium will be trans to the carbomethoxy moiety and can in no way undergo intramolecular lactonization.

In view of the foregoing discussion the formation of 116 from 114 can also be explained by the assigned stereochemistry of 114 hence that of 96 according to the scheme III. Thus tosylation of 114 afforded the intermediate tosylate 114a. An intramolecular displacement of the p-toluenesulfonyl moiety leading to the intermediate 114b can only occur if the two cyclopentane rings are trans or anti to each other as shown in structure 114b. This will lead to the sulfonium intermediate 114c. Deprotonation of 114c then afforded the observed product 116.

By a similar reasoning the formation of 115 in the reduction of 96 with lithium aluminum hydride can also be explained by scheme IV. Thus reduction of the ester moieties of 96 would lead to an intermediate aluminum complex 115a in which the alkoxydihydroaluminum can function as an internal Lewis acid. This intramolecular complexation leading to 115b can occur if the two cyclopentane rings are trans or anti to each other. The complex 115b can collapse to give the sulfonium intermediate 115c. Once again an intramolecular interception of the sulfonium ion by the oxygen of the alkoxyaluminum complex leading to 115d and

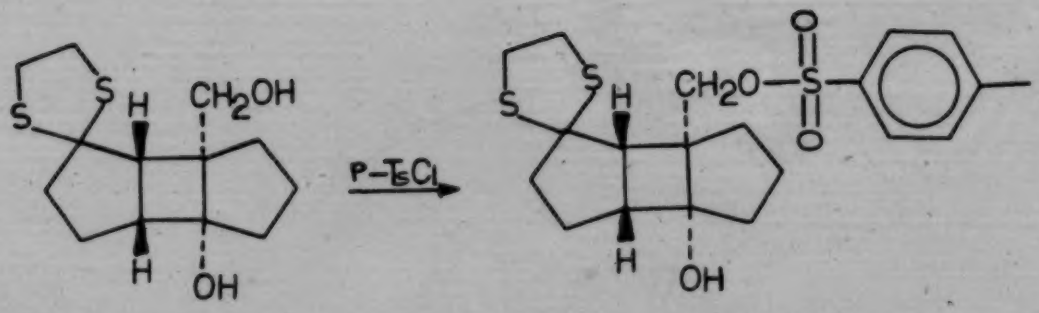
then 115e can only occur if the two cyclopentane rings are trans to each other. Further reduction of the oxonium intermediate 115e by lithium aluminum hydride from the sterically less hindered side would then afford 115.

The observed results are therefore in agreement with the aforementioned rationalizations, hence the assignment of the stereochemistry of 101 and 102.

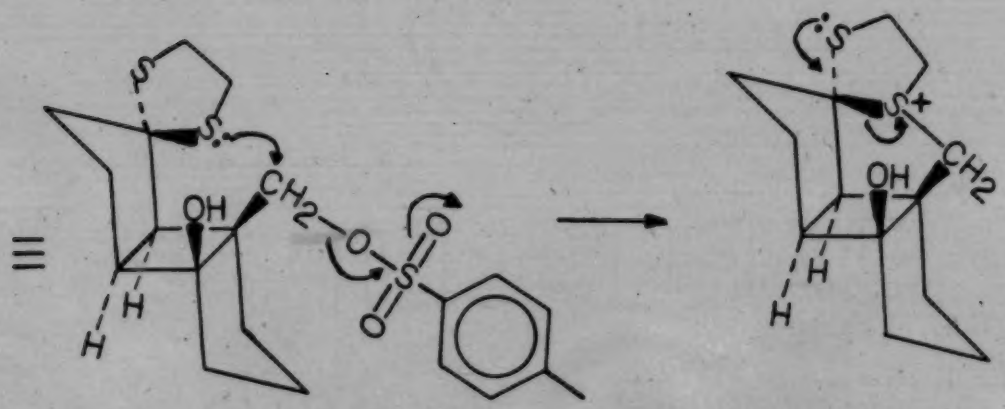
From these results on structural elucidation it can be seen that the structure and stereochemistry of the photocycloadducts and their thioketal derivatives have been clearly established.

As already pointed out 126 was envisaged as a useful intermediate for the synthesis of zierone. The carbomethoxy group would eventually be converted into the C-10 methyl group, and since its stereochemistry is known, the stereochemistry of the C-10 methyl group relative to the C-1 hydrogen can be clearly defined. Secondly, the formation of 134 and 135 and subsequently 136 and 137 in high yields showed that these intermediates could be used in studies towards the synthesis of zierone. Thirdly the hydroazulenone 106 also has attractive features as an intermediate in the synthetic studies of zierone in view of its facile formation from 95 and 97. Synthetic studies employing these intermediates were all investigated. Thus the use of the thioketalized photocycloadducts 95 and 97 as starting materials was investigated. The use of the photocycloadducts 103 and 104 as starting compounds was also investigated. Finally the

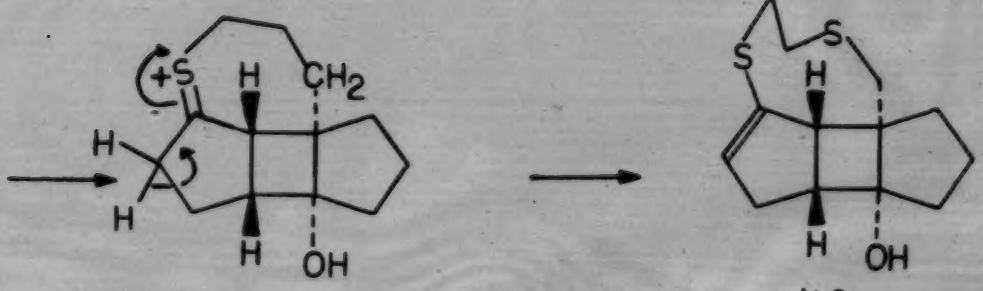
SCHEME III



114 114a

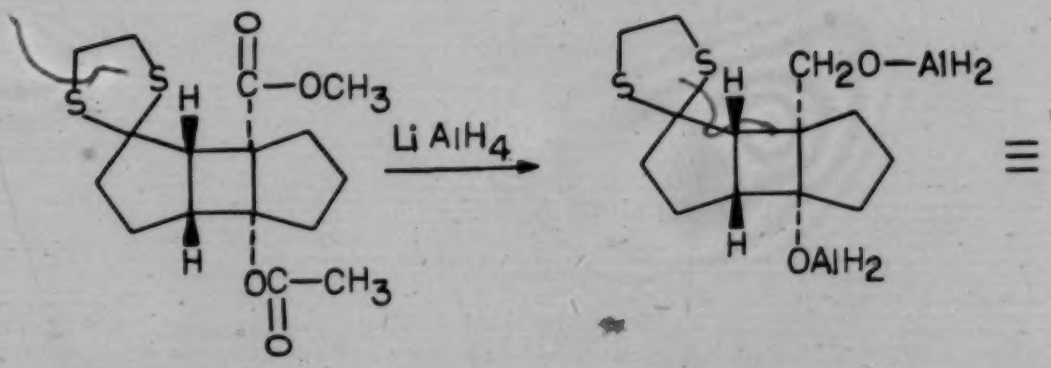


114a 114b

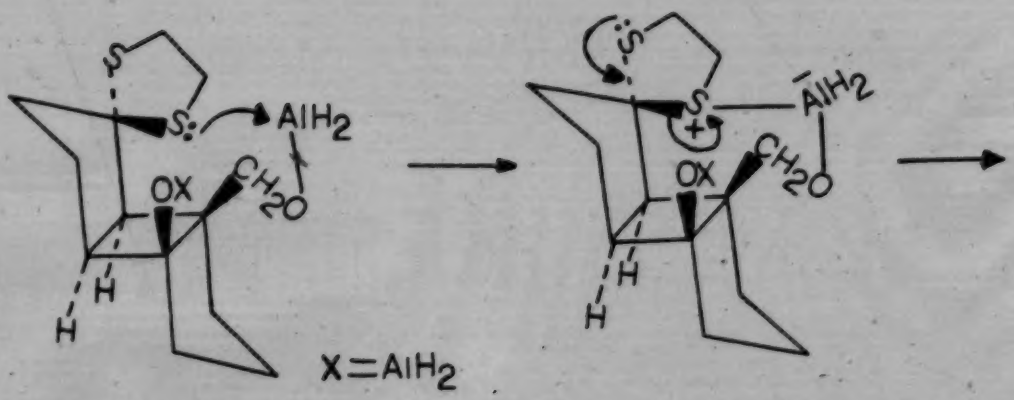


114c 116

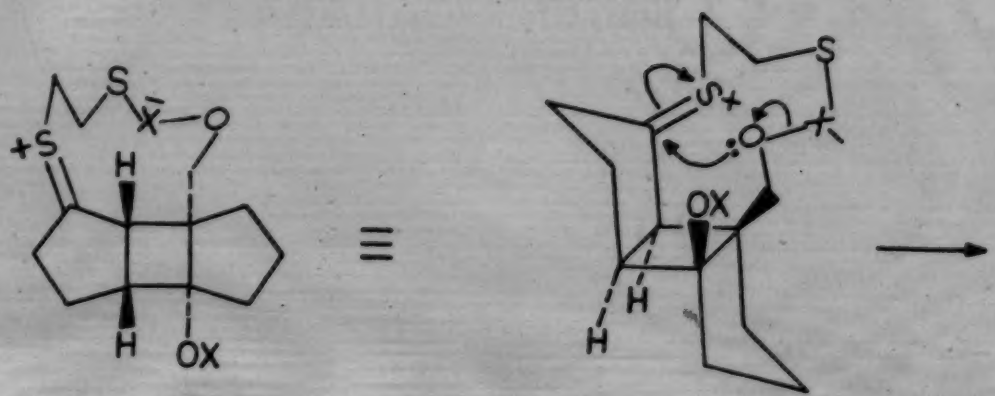
SCHEME IV



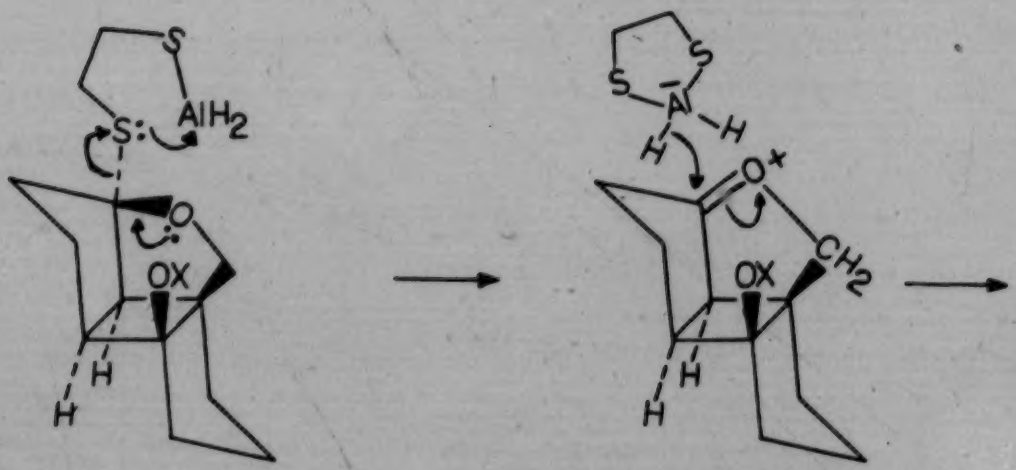
96 115a



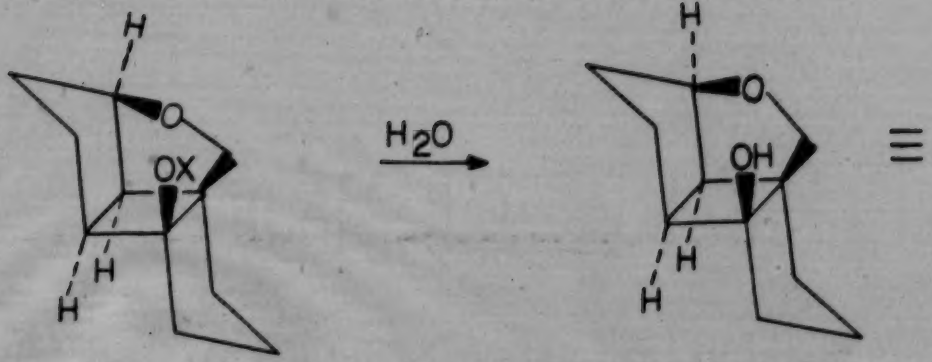
115a 115b



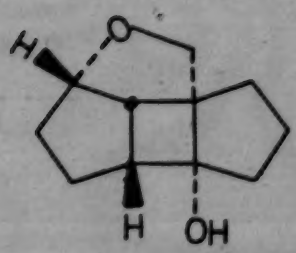
115c 115c



115d 115e



115f 115



115

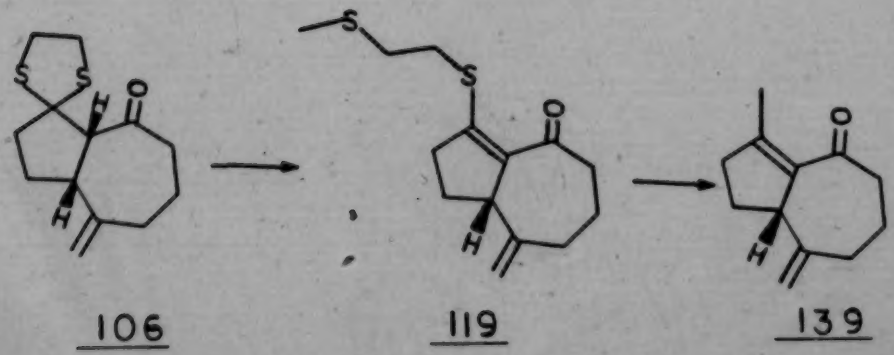
use of the photocycloadducts 101 and 102 as starting compounds was also undertaken and these synthetic studies constitute the subject matter of the subsequent chapters.

CHAPTER III: APPROACHES TO ZIERONE VIA THE HEAD-TO-HEAD PHOTOCYCLOADDUCTS

It has been shown that the thioketalized photocycloadducts 95 and 97 constitutes approximately 51% of the product mixture when benzene was used as solvent in the initial photocycloaddition reaction. It was also shown that both diastereomers could be converted into the same unsaturated ketone 106 by reduction of the ester moieties with lithium aluminum hydride to afford the corresponding diols 105 and 117, followed by treatment of the diols with p-toluenesulfonyl chloride in pyridine. It was thought that the ketone 106 could be converted into the dienone 139 and thence to the enone 131. The enone 131 was considered as a key intermediate target molecule which has the correct stereochemistry at the C-1 and C-10 centres with respect to zierone, and has its C-6 position appropriately functionalized for the introduction of the isopropylidene group and for further elaboration to give zierone as shown in scheme V.

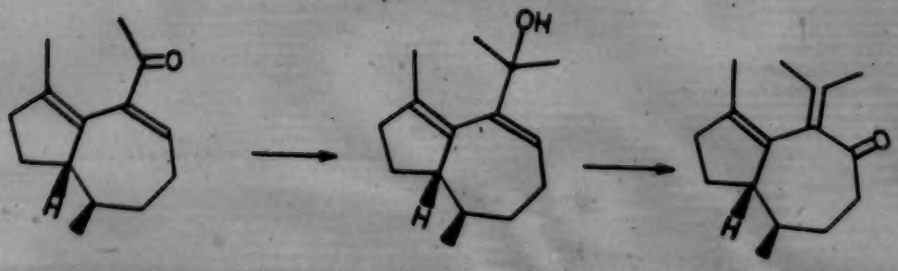
It was further shown that hydrolysis of the thioketalized adducts 95 and 97 with mercuric chloride afforded the corresponding keto-diesters 103 and 104. Treatment of these keto-diesters with methyllithium, followed by treatment of the products with sodium methoxide afforded the unsaturated keto-ester 126. The keto-ester 126 could also be converted into the key intermediate enone 131. (scheme VI). Efforts directed towards the use of the keto-diesters 103 and 104 (Head-to-Head adducts) and their respective thioketals 95 and 97 in the formation of the key intermediate enone 131 and the subsequent conversion of 131 into zierone

SCHEME V



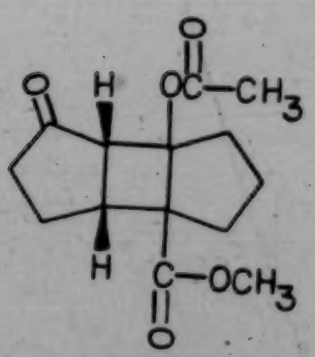
106 119 139

131 140

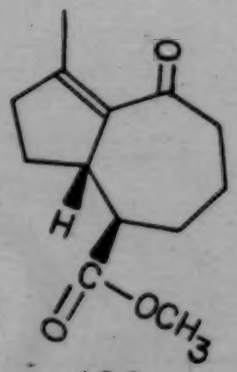


141 142 1

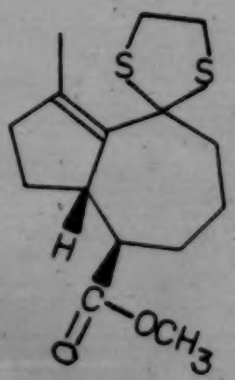
SCHEME VI



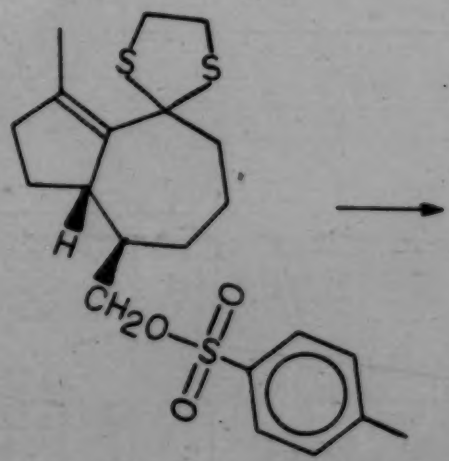
103 OR 104



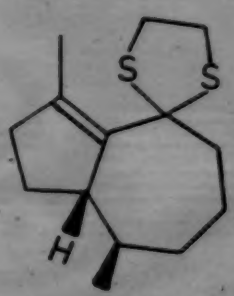
126



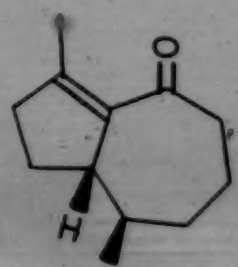
160



166



168

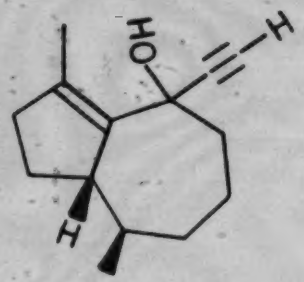


131

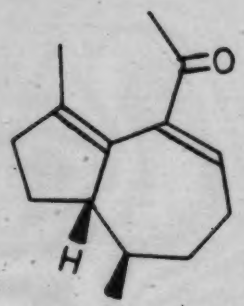
are presented in this chapter.

It was thought that the unsaturated ketone 106 could be converted into 139 and thence to 131. Towards this end the unsaturated ketone 106 was treated with sodium hydride in dry dimethoxyethane followed by alkylation of the incipient mercapto group with methyl iodide to give the dienone 119 in 86.5% yield. The dienone 119 was treated with lithium dimethyl cuprate with the aim of forming the ketone 143 which could be converted into 139 by elimination of the sulfur containing group, however this effort was futile. Instead of the desired Michael addition reaction, the undesired 1,2-addition reaction occurred with an accompanying cyclization to give the tricyclic ether 138. The formation of the cyclic ether could have occurred via cyclization of the incipient alchoxide with the exocyclic double bond prior to the workup of the product. This presumably can occur via coordination of the exocyclic double bond to copper thereby activating the double bond for cyclization. The formation of the cyclic ether could also have occurred via cyclization of the alcohol, produced during the workup, with the exocyclic double bond. The pmr spectrum of 138 showed resonance signals at δ 2.25 (s, 3H) for the (-S-$\underline{CH_3}$) methyl protons, δ 2.88-3.0 (m, 4H) for the (-S-$\underline{CH_2}$-$\underline{CH_2}$-S-) methylene protons and at δ 1.28 (s, 6H) for the protons of the two methyl groups flanking the ether linkage. It was reasoned that perhaps the β-substituent was bulky and was therefore interacting sterically with the incoming methyl group or

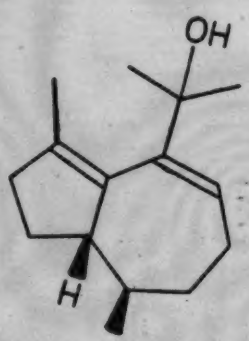
that the vinylic sulfur atom was participating in the reaction by donating an electron via the carbon-carbon π-bond to the ketonic oxygen in the presence of the cuprate reagent and the resulting α,β-unsaturated sulfonium ion 119a then reacted in the usual Michael fashion followed by cyclization to give 138. It was therefore thought that by replacing the sulfur containing substituent with a methoxy group this problem could be eliminated. Consequently the dienone 119 was heated under reflux in methanolic sodium methoxide to give 144 quantitatively. The pmr spectrum collaborated this structure with signals at δ 4.85 (s, 2H) for the vinylic methylene protons ($-\underline{C}=\underline{CH_2}$), δ 4.1 (s, 3H) for the methoxy methyl protons, δ 2.13 (s, 3H) for the ($-S-\underline{CH_3}$) methyl protons and at δ 2.85 (s, 4H) for the ($-S-\underline{CH_2}-\underline{CH_2}-S-$) methylene protons. The infrared spectrum showed a saturated seven-membered ring ketone absorption at 1700 cm^{-1}. Unfortunately however, treatment of 144 with methyl iodide to form the sulfonium salt followed by treatment with sodium hydride did not give the desired product 144a but the precursor 119. As 139 could not be obtained by the envisaged direct transformations, the ketone function of 119 was reduced with sodium borohydride in methanol with the aim of forming 145, which could be hydrolysed, followed by dehydration to give the dienone 146. Grignard reaction of 146 with methylmagnesium bromide or methyllithium could afford 147, the hydroxy group of which could be rearranged with concomittant oxidation to afford 139. Here again the



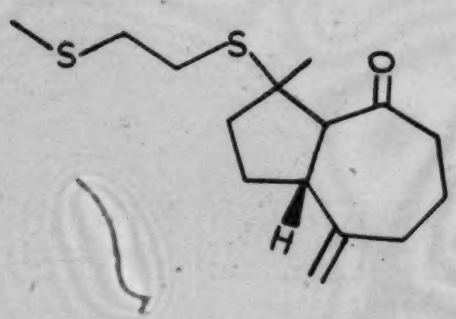
140



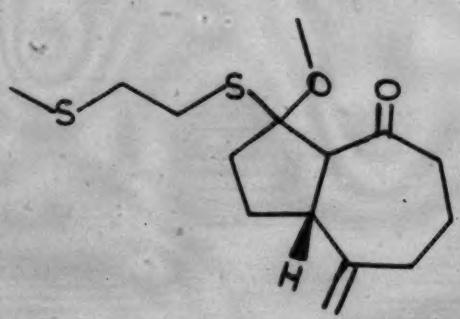
141



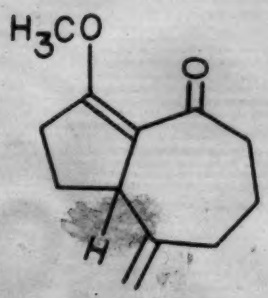
142



143

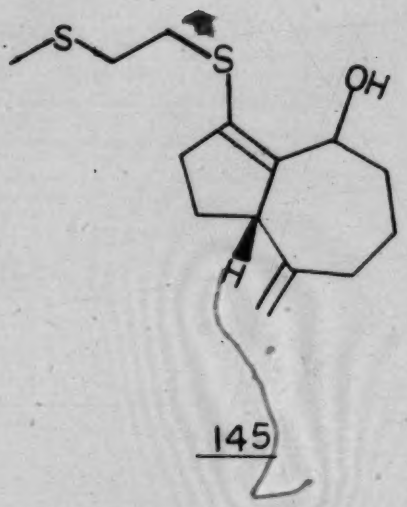


144

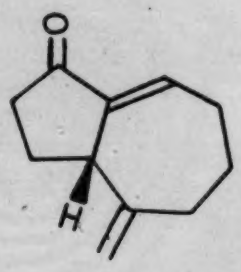


144a

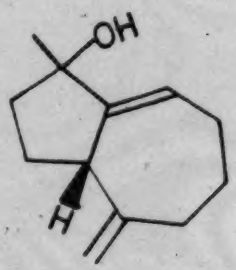
desired product was not formed, instead the dehydrated product 148 was the only isolated product. The infrared spectrum of 148 showed a carbon-carbon double bond absorption of medium intensity at 1645 cm^{-1}, while the pmr spectrum indicated signals at δ 5.88 (t, 1H, J = 2 Hz) for the C-3 vinylic proton, δ 5.78 (1H) for the C-6 vinylic proton, δ 5.80 (d, 2H, J = 12 Hz) for the exocyclic methylidene protons, δ 3.75 (m, 1H) for the C-1 proton, δ 2.18 (s, 3H) for the (-S-CH_3) methyl protons and at δ 2.7 (m, 4H) for the (-S-CH_2-CH_2-S-) methylene protons. The mass spectrum gave a molecular weight of 252.1007 for $C_{14}H_{20}S_2$ in support of the assigned structure. Although reduction of 119 with lithium aluminum hydride in diethyl ether at 0°C led to the formation of the desired alcohol 145, attempts at purification of the alcohol by column chromatography on silica gel again led to dehydration with the formation of 148. However reduction followed by acetylation with acetyl chloride without isolation of the intermediate alcohol afforded 149 purification of which by column chromatography on silica gel resulted in the elimination of acetic acid to give 148 again, in 60% yield, and the rearranged product 150, in 10% yield and the isolated acetate 149 in 30% yield. On the other hand purification by column chromatography on alumina grade II afforded the acetate 149 in 60% yield and the elimination product 148 in 40% yield. All of the products were analyzed to ascertain their structure and composition. Thus, the infrared spectrum of 149 showed a



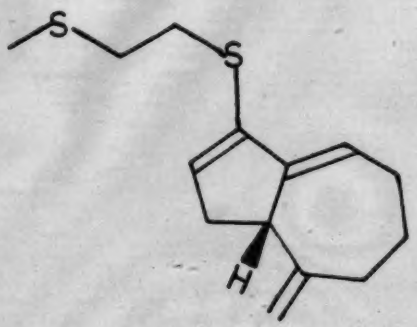
145



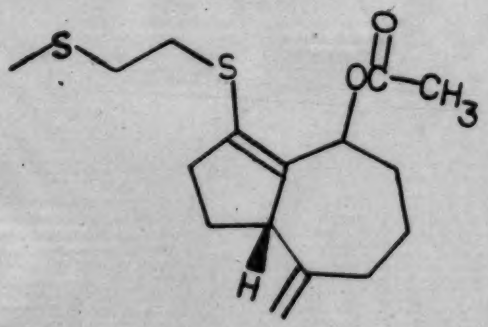
146



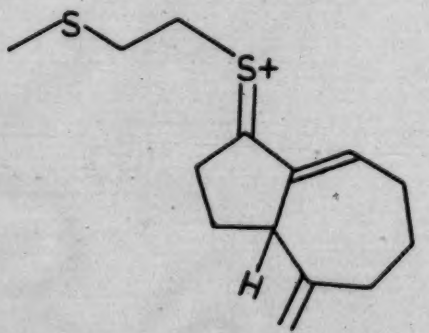
147



148



149



149a

strong carbonyl absorption at 1725 cm^{-1} due to the acetoxy group and a carbon-carbon double bond absorption at 1640 cm^{-1}. The pmr spectrum showed resonance absorptions at δ 2.1 (s, 3H) for the acetoxy methyl protons, δ 2.15 (s, 3H) for the (-S-$\underline{CH_3}$) methyl protons, δ 4.8 (s, 2H) for the exocyclic methylidene protons, δ 3.58 (t, 1H, J = 9 Hz) for the C-1 doubly allylic proton, δ 5.05 (t, 1H, J = 6 Hz) for the proton on the carbon bearing the acetoxy group, δ 2.6 (m, 4H) for the (-S-$\underline{CH_2}$-$\underline{CH_2}$-S-) methylene protons and at δ 2.9 (m, 4H) for the remaining allylic protons in both rings. The mass spectrum gave a molecular ion peak of 312.1201 in support of the molecular formula of $C_{16}H_{24}O_2S_2$ in addition to a more prominent m/e peak at 252.1007 corresponding to $C_{14}H_{20}S_2$, with the loss of acetic acid. In pursuance of the intermediate dienone 146 both ester derivatives 149 and 150 were treated with mercuric chloride in acetonitrile-water mixture at room temperature to give 146 in a total of 65% yield. However when the triene 148 was similarly treated it did not react at all and produced 146 in 20% yield only upon heating to 50°C. In view of the ease of formation of 148 from the unsaturated ketone 119, further efforts were made to convert 148 into the desired dienone 146 by treatment with titanium tetrachloride in aqueous acetonitrile and also in aqueous acetic acid but only the isomeric dienone 151 was formed quantitatively. The facile hydrolysis of the ester derivatives 149 and 150 as opposed to the lack of reactivity of 148 under identical conditions

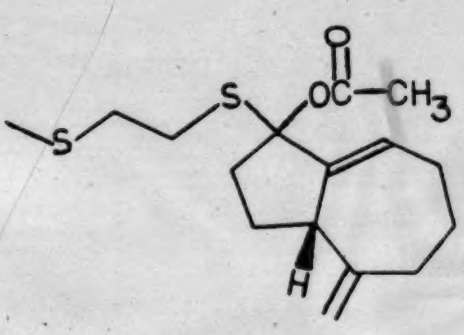
is attributed to the presence of the acetoxy group which presumably facilitates the formation of the intermediate 149a via elimination of the acetate moiety. Interception of this sulfonium intermediate by water then afforded the ketone 146.** The infrared spectrum of 146 contained two strong absorptions at 1715 cm^{-1} assigned to the α,β-unsaturated five-membered ring ketone carbonyl and at 1645 cm^{-1} for the carbon-carbon double bonds. The pmr spectrum showed resonance signals at δ 4.82 (m, 2H) for the exocyclic methylidene protons, 6.8 (m, 1H) for the vinylic proton beta to the ketone functionality, 3.5 (m, 1H) for the doubly allylic C-1 proton. The multiplicity observed for all of the signals could be attributed to the expected couplings to the adjacent protons in addition to long range coupling between the doubly allylic C-1 proton and the vinylic protons. The mass spectrum also gave a molecular ion peak of 162.1043 corresponding to the molecular formula of $C_{11}H_{14}O$. Although the desired dienone 146 could be obtained from the ketone 106 as shown above, the overall conversion was obviously not satisfactory and it was clear that an alternative approach to 146 would be desirable. The easily accessible ketone 106 appeared to be potentially useful as a precursor of the dienone 146, as reduction of

---

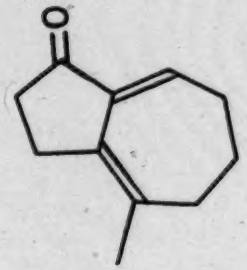
** Since the difficulties leading to the low yield of the dienone 146 stemmed from elumination of acetic acid during the purification of the acetate 149, the crude acetate 149 was hydrolysed with mercuric chloride but the dienone 146 was formed in only 20% yield.

the ketone function was expected to afford the alcohol 152, the thioketal moiety of which could be hydrolyzed to the ketone with in situ or subsequent dehydration to afford 146. It was however disappointing to find that reduction of 106 with lithium aluminum hydride in ether or with sodium borohydride in methanol did not form the desired product but rather the cyclic ether 153 in near quantitative yield. The infrared spectrum of the reduction product 153 showed no hydroxyl or carbonyl absorption while its pmr spectrum showed resonance signals at δ 1.16 (s, 3H) for the C-7 methyl protons, δ 4.40 (m, 1H) for the C-1 proton α to the oxygen atom of the tetrahydrofuran ring and δ 3.25 (br. s, 4H) for the (-S-CH_2-CH_2-S-) methylene protons of the thioketal group. The mass spectrum also agreed with the assigned structure with a molecular weight of 256.1202 corresponding to $C_{13}H_{20}OS_2$.

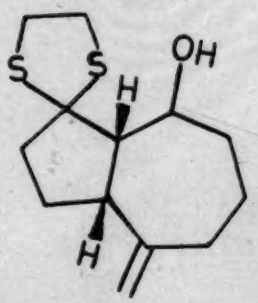
The thioketal moiety of the cyclic ether 153 was hydrolysed with mercuric chloride in aqueous acetonitrile to afford the keto-ether 154 in quantitative yield. It was thought that β-cleavage of the ether linkage could give the hydroxy-ketone 155 which could in principle be dehydrated to give the dienone 146. The infrared spectrum of 154 showed a strong absorption at 1740 cm^{-1} for the cyclopentanone carbonyl group and its pmr spectrum showed resonance signals at δ 1.32 (s, 3H) for the C-7 methyl protons and δ 4.38 (br. s, 1H) for the proton adjacent to the oxygen atom of the ether linkage, while the mass



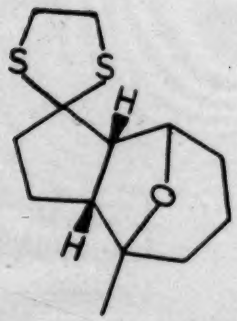
150



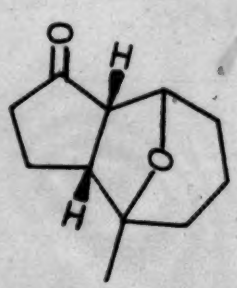
151



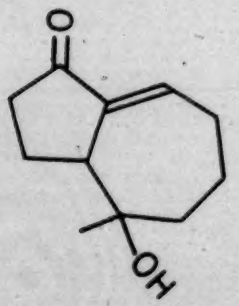
152



153

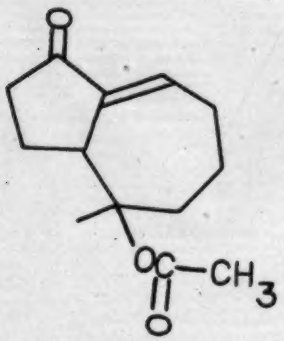


154

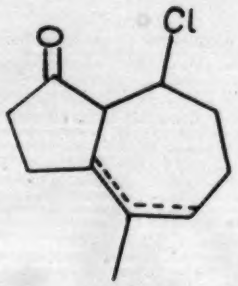


155

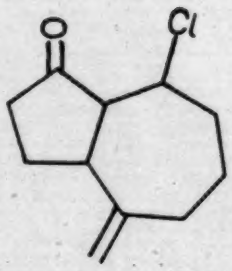
spectrum gave a molecular weight of 180.1112 for $C_{11}H_{16}O_2$. The ether linkage βeta to the ketone carbonyl was cleaved[54] by treatment of 154 with acetic anhydride in pyridine to give three products, 146 in 39% yield, 151 in 20% yield and 156 in 30% yield. On the other hand when 154 was added to a slurry of acetyl chloride in pyridine for fourty hours at room temperature an inseparable mixture of products was obtained. The infrared and pmr spectra suggested the presence of 157 and 158. The product mixture was therefore treated with methanolic sodium hydroxide at room temperature to afford the dienone 146 in 45% yield after separation by column chromatography on silica gel. The rather low yields of the desired product 146 was disappointing and efforts to convert it into the ketone 139 were even more so. Upon treatment of 146 with methyllithium two isomeric alcohols 147 were obtained in 95% yield in a ratio of 1:1, however when both-alcohols were treated with pyridinium chlorochromate in methylene chloride to effect a 1,3 sigmatropic rearrangement of the hydroxy group followed by in situ oxidation of the resulting C-6, secondary alcohol only 20% yield of 139 was obtained. The infrared spectrum of 139 showed a carbonyl absorption at 1670 cm^{-1} for the cycloheptanone carbonyl group conjugated to the double bond, and a carbon-carbon double bond absorption at 1608 cm^{-1}. The proton magnetic resonance spectrum showed resonance peaks at δ 4.75 (2H) for the vinylic protons, δ 2.04 (s, 3H) for the vinylic methyl protons and δ 3.50 (br. m, 1H) for the C-1 doubly allylic



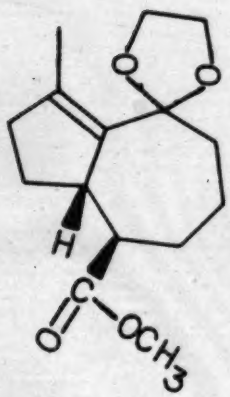
156



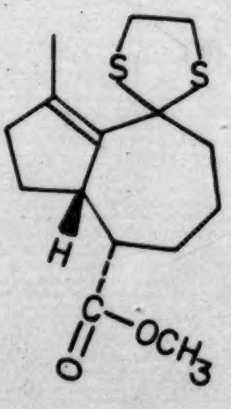
157



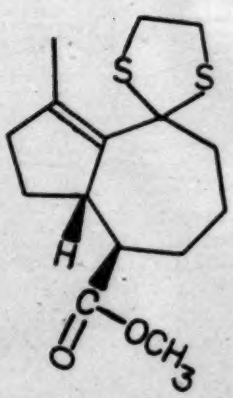
158



159



160



161

proton. This unexpected low yield of 139 coupled with the low yield in the conversion of 119 into the dienone 146 made the use of 106 less attractive. It became even less attractive when it was considered that conversion of the methylidene group into a methyl group could lead to epimers at the C-10 centre thereby affording a very low yield of the key intermediate enone 131. An alternative approach to 131 was therefore absolutely necessary if an efficient total synthesis of zierone was to be achieved.

The use of the head-to-head keto-diesters 103 and 104 instead of their respective thioketals was therefore exhaustively explored towards the synthesis of the key intermediate ketone 131 as outlined in scheme VI. It has already been shown that the keto-diester 104 could be converted into the enone-ester 126 and that 103 could also be converted into 126 and its C-10 epimer 130. It was also pointed out that the stereochemistry assigned to 126 and 130 was correct, and their correctness would be shown later by their conversion into 131 and 132 respectively. Further conversion of 131 into zierone or of 132 into epi-zierone could be achieved by following the previously designed route shown in scheme V. As 126 already contained the desired α,β-unsaturated ketone functionality, the problem of low yields encountered in the rearrangement of 147 to 139 had been avoided. Secondly the stereochemistry of the carbomethoxy group in 126 and consequently of the C-10 methyl group of zierone has also been established relative to the

C-1 centre, and this approach therefore provided a good control of the stereochemistry of the two chiral centres in zierone.

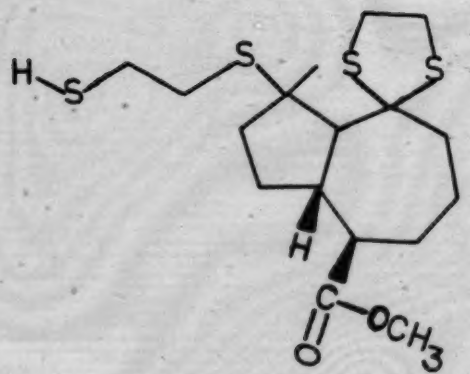
As the ketone functionality of 126 would be utilized to introduce the isopropylidene group of zierone, it was necessary to protect this functionality while the carbomethoxy group was being converted into a methyl group. The use of ethyleneglycol to form the ketal 159 was found to be unsuitable due to the rapid reversion of 159 to 126 in the presence of water during the isolation of 159. However the thioketal 161 proved to be a better choice with respect to stability. When 126 was stirred with twenty equivalents of 1,2-ethanedithiol in methylene chloride at room temperature and boron trifluoride etherate added as catalyst it afforded, 161 in 58% yield and 162 in 27% yield. However when the amount of the dithiol was reduced to five equivalents and the reaction carried out at -15°C the yield of the desired thioketal 161 was increased to 80% and 162 was formed in only 20% yield. The infrared spectrum of 161 showed a strong carbonyl absorption for the ester group at 1730 cm^{-1}. The pmr spectrum portrayed resonance signals at δ 3.65 (s, 3H) for the ester methyl protons, δ 2.02 (s, 3H) for the vinylic methyl protons and δ 3.1-3.5 (m, 4H) for the thioketal methylene protons, while its mass spectrum gave a molecular weight of 298.1052 for $C_{15}H_{22}O_2S_2$. It should be pointed out at this stage that although our objective was directed towards the synthesis of zierone we also became

interested in epi-zierone (26) at this point mainly for the purpose of comparison due to the availability of the enone-ester 130. The epimeric thioketal 160 was similarly prepared from the enone-ester 130 as it can be seen that 130 has the stereochemistry at the C-1 and C-10 centres corresponding to epizierone. Its spectral data [ir 1730 cm^{-1} for the ester carbonyl, pmr, δ 1.98 (s, 3H) for the vinylic methyl protons, δ 3.62 (s, 3H) for the ester methyl protons δ 3.2-3.5 (m, 4H) for the thioketal methylene protons, mass spectrum, 298.1052 for $C_{15}H_{22}O_2S_2$], parallels those assigned for 161 showing them to be stereoisomers. The epimer of 162 was also formed in 20% yield and identified as 163. The ester functionality of the thioketal-ester 161 was reduced with lithium aluminum hydride in diethyl ether to afford the primary alcohol 164 in 94% yield. The infrared spectrum showed a hydroxyl absorption band at 3605 cm^{-1} and 3450 cm^{-1} and a weak carbon-carbon double bond absorption at 1670 cm^{-1}. The pmr spectrum showed resonance signals at δ 1.96 (s, 3H) for the vinylic methyl protons, δ 3.45-3.6 (m, 2H) for the methylene protons of the hydroxymethyl group, δ 3.0-3.45 (m, 4H) for the thioketal (-S-CH_2-CH_2-S-) methylene protons, in addition to the signals of the remaining protons at δ 1.3-3.0 (m, 13H). The mass spectrum gave a molecular weight of 270.1111 for $C_{14}H_{20}OS_2$. The isomeric alcohol 165 was also obtained in 95% yield by similarly treating 160 with lithium aluminum hydride. The spectral data obtained for 165, [IR ($CHCl_3$) 3605 cm^{-1} and 3450 cm^{-1}, pmr δ 1.98 (s, 3H)

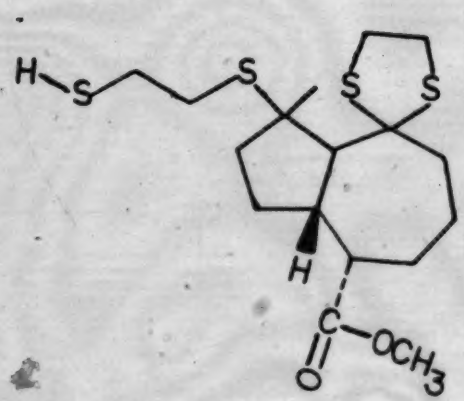
vinylic methyl protons, δ 3.45-3.7 (m, 2H) methylene protons of the hydroxymethyl group, δ 3.0-3.4 (m, 4H) thioketal methylene protons and δ 1.3-3.0 (m, 13H) for the rest of the protons] also paralleled those of 164, while the mass spectrum showed a molecular ion peak at 270.1111 in agreement with the expected molecular formula of $C_{14}H_{20}OS_2$. Tosylation of the alcohol functionality was achieved by treatment of 164 with p-toluenesulfonyl chloride in pyridine to afford the sulfonate 166 in 98% isolated yield. The pmr spectrum supplied all the information needed to characterise 166. It showed the aromatic protons as an AB quartet at δ 7.35 (d, 2H, J = 8 Hz); 7.8 (d, 2H, J = 8 Hz). It also showed resonance signals at δ 4.05 (d, 2H, J = 6 Hz), for the methylene protons of the sulfonate ester functionality, δ 3.2-3.6 (m, 4H) for the thioketal methylene protons (-S-$\underline{CH_2}$-$\underline{CH_2}$-S-), δ 2.46 (s, 3H) for the toluenesulfonate methyl protons and at δ 2.0 (s, 3H) for the vinylic methyl protons. The mass spectrum also portrayed a molecular ion peak of 424.1205 in conformity with the assigned molecular formula of $C_{21}H_{28}O_3S_3$. Similarly, treatment of 165 with p-toluenesulfonyl chloride in pyridine afforded the isomeric p-toluenesulfonate 167 in 95% yield. [Pmr: δ 1.90 (s, 3H) for the vinylic methyl protons, δ 2.42 (s, 3H) for the p-toluenesulfonate methyl protons, δ 3.1-3.6 (m, 4H) for the thioketal methylene protons (-S-$\underline{CH_2}$-$\underline{CH_2}$-S-), δ 3.9, (d, 2H, J - 6 Hz) for the methylene protons of the sulfonate ester moiety (-$\underline{CH_2}$-O-SO_2-), δ 7.34 (d, 2H, J = 8 Hz), δ 7.78 (d, 2H,

J = 8 Hz) for the aromatic protons and δ 1.2-3.1 (m, 12H) for the rest of the protons, while the mass spectrum gave a molecular weight of 424.1205 as expected for $C_{21}H_{28}O_3S_3$].

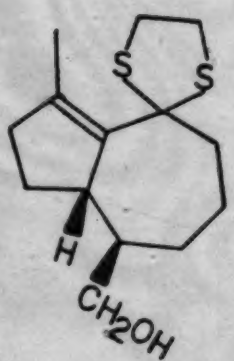
The toluenesulfonate group was reductively cleaved by the treatment of 166 and 167 with lithium aluminum hydride in diethyl ether to afford 168 and 169 respectively in 85% yield each. The pmr spectrum of 168 showed resonance absorptions at δ 1.98 (s, 3H) for the vinylic methyl protons, δ 3.1-3.6 (m, 4H) for the thioketal methylene protons, δ 0.96 (d, 3H, J = 5 Hz) for the C-10 methyl protons and δ 1.2-3.1 (m, 12H) for the remaining protons of the carbocyclic system. The mass spectrum gave a molecular weight of 254.1164 corresponding to the assigned molecular formula of $C_{14}H_{22}S_2$. The pmr spectrum of 169 also showed resonance signals at δ 1.97 (s, 3H) for the vinylic methyl protons, δ 0.76 (d, 3H, J = 6 Hz) for the C-10 methyl protons, δ 3.2-3.6 (m, 4H) for the thioketal methylene protons (-S-$\underline{CH_2}$-$\underline{CH_2}$-S-) and δ 1.15-3.0 (m, 12H) for the remaining protons of the carbocyclic system, thus characterising this compound as an isomer of 168. Its mass spectrum also gave a molecular weight of 254.1164 in agreement with the assigned molecular formula of $C_{14}H_{22}S_2$. The thioketal moieties of 168 and 169 were hydrolyzed with mercuric chloride in aqueous acetonitrile to afford the α,β-unsaturated ketones 131 and 132 respectively in 54% yield each. However when diethyl ether was used as co-solvent to increase the solubility of the thioketals, the yield of the hydrolysis products was increased to 75% each.



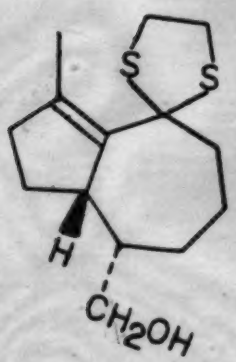
162



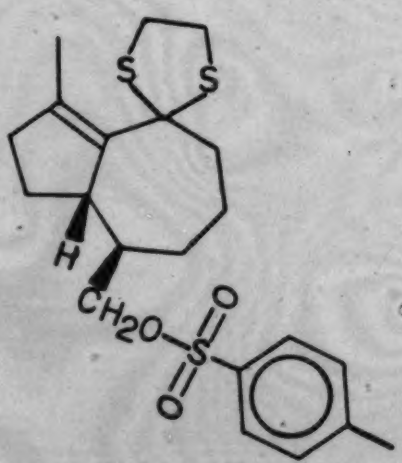
163



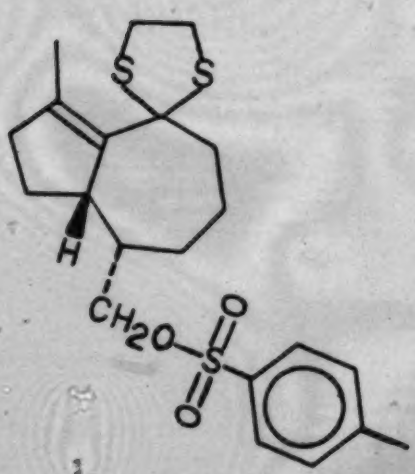
164



165



166



167

The infrared spectrum of 131 showed an intense carbonyl absorption at 1680 cm^{-1} and a strong absorption of the carbon-carbon double bond in conjugation with the carbonyl group at 1610 cm^{-1}. The proton magnetic resonance spectrum showed absorptions at δ 2.02 (s, 3H) due to the vinylic methyl protons, δ 0.96 (d, 3H, J = 5 Hz) for the C-10 methyl protons and at δ 1.2-2.7 (m, 12 H) for the carbocyclic ring protons. The mass spectrum gave a molecular ion peak at 178.1359 in agreement with the assigned molecular formula, $C_{12}H_{18}O$. The spectral data for 132 once again paralleled those of 131. Its infrared spectrum showed an intense carbonyl absorption at 1680 cm^{-1} and a strong absorption due to the carbon-carbon double bond in conjugation with the ketone functionality at 1610 cm^{-1}. The pmr spectrum showed resonance signals at δ 2.08 (s, 3H) for the vinylic methyl protons, δ 0.77 (d, 3H, J = 6 Hz) for the C-10 methyl protons, δ 3.1-3.4 (m, 1H) for the C-1 allylic proton and at δ 1.3-2.6 (m, 11H) for the rest of the carbocyclic ring protons, while the mass spectrum portrayed a molecular ion peak at 178.1359 for $C_{12}H_{18}O$. It can clearly be seen from the foregoing chemical reactions and the spectral properties of 131 and 132 and their precursors that they are indeed isomers. It is obvious that none of the chemical reactions involved in the conversion of the enone-esters 126 and 130 into enones 131 and 132 respectively could possibly epimerize the C-10 centre, therefore, the relative stereochemistry of the C-1 and C-10 centres of the latter two

compounds are the same as those of their respective ester precursors, 126 and 130. The assignment of the stereochemistry of 126 and 130 was based on experimental evidence as well as theoretical considerations.

It was observed that fragmentation of the cyclobutane ring of the diester 123 with 0.20M methanolic sodium methoxide afforded only one product, 126. Furthermore, treatment of 130, the epimer of 126, with 0.20M methanolic sodium methoxide did not afford any of 126. This established that 126 and 130 were not interconvertible under the reaction conditions and that none of 130 was formed during the fragmentation of 123. This disproved any assumption that some of 130 was formed but was converted into 126 under the reaction conditions. This also meant that as soon as the fragmentation intermediate carbanion is formed it was irreversibly protonated, otherwise some of the isomer 130 would have been formed via epimerization of the C-10 centre. Interestingly and more importantly, it was also observed that when either 126 or 130 was treated with two equivalents of lithium diisopropylamide in ether at -78°C (under aprotic conditions) and the resulting dianion was quenched with aqueous ammonium chloride a mixture of 126 and 130 was obtained in a ratio of 1.5:1 (126:130) irrespective of the starting compound. This suggested that kinetic protonation from the face of the molecule anti to C-1 ring junction proton was faster than from the face syn to the C-1 proton. It also pointed out the fact that after fragmentation of the four-membered ring

in the reaction of 103 with methyllithium, the incipient C-10 carbanion formed survived long enough to epimerize before protonation thereby leading to the epimeric compounds 126 and 130. It has been observed by Kupchan et al.[55] that the C-10 substituent of the 1,10-anti isomer (C-10 substituent trans to the C-1 proton) is spatially close to and spectroscopically shielded by the sp^2-hybridized C-6 centre in hydroazulenes with a C-6 sp^2 centre. This observation, when extrapolated and applied to the intermediate C-10 carbanion or the transition state leading to 126 and 130 from the reaction of 103 with methylithium or the epimerization of 126 and 130 with lithium diisopropylamide would lead to the prediction that the lone paired 2p orbital of the incipient carbanion or transition state would prefer an anti relationship to the C-1 proton in order to achieve a situation of maximum overlap or interaction (low energy state) with the C-6 sp^2 π-orbitals. This requirement would lead to the formation of 126 as a major product compared to 130. This theoretical consideration would also support our assertion that protonation leading to 126 would be faster than protonation leading to 130 as the former would have a lower energy barrier. As a result of these stereo-electronic considerations the stereochemistry of 126 was assigned to the major epimerization product and the stereochemistry of 130 was assigned to the minor epimerization product. Finally it would be expected from the foregoing reasoning that the C-10 methyl group of 131, implying the

stereochemistry of 126 would not be shielded by the C-6 sp^2 centre while the C-10 methyl group of 132 would be shielded, and this was found to be the case. It was therefore concluded that 131 having the C-10 methyl group absorption at δ 0.96 in its pmr spectrum has its C-10 methyl group syn to the C-1 proton and 132 having its C-10 methyl group absorption at δ 0.77 has the methyl group anti to the C-1 proton. It should be mentioned here that the 1,10-syn-hydroazulenone 131 [C-1 H syn to C-10 CH_3] is particularly valuable because several naturally occurring guainolides[56-58] possess the 1,10 Syn stereochemistry and hydrogenation of C-10 olefinic hydroazulenes lead mainly to 1,10-anti products.[59] While attempts were being made to convert 131 into zierone, Posner and Loomis published a synthesis of 131 and 132 via an independent route and to our delight, their results were in agreement with our assigned structures.

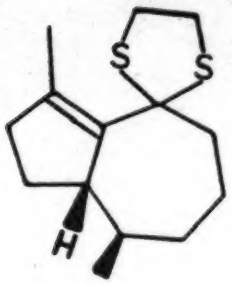
It was mentioned that 162 and 163 were formed in 20% each during the formation of the thioketals 126 and 130 respectively. These products were analyzed and efforts were made to convert 162 into 131 in order to improve the total conversion of 126 into 131. The infrared spectrum of 162 showed a single strong carbonyl absorption at 1725 cm^{-1} for the ester group, while its pmr spectrum portrayed signals at δ 1.70 (s, 3H) for the C-4 methyl protons, δ 3.67 (s, 3H) for the carbomethoxy methyl protons, δ 3.2-3.5 (m, 4H) for the (-S-CH_2-CH_2-S-) open chain methylene protons, and δ 2.6-2.9 (m, 4H) for the thioketal methylene

protons. The mass spectrum gave a molecular weight of 392.0972 corresponding to $C_{17}H_{28}O_2S_4$ in agreement with the assigned structure. The spectral data of 163 was also similar to that of 162. The infrared spectrum showed a strong absorption at 1725 cm^{-1} diagnostic of the ester functionality. The pmr spectrum showed resonance signals at δ 1.74 (s, 3H) for the C-4 methyl protons δ 3.22-3.50 (m, 4H) for the (-S-CH_2-CH_2-S-) open chain methylene protons, δ 1.2-3.0 (m, 18H) for the thioketal methylene protons and the rest of the protons of the molecule, while its mass spectrum also gave a molecular ion peak at 392.0972 for $C_{17}H_{28}O_2S_4$. Upon reduction of 162 with lithium tetrahydroaluminate in diethyl ether, it afforded 54% yield of the desired alcohol 170, which showed the hydroxyl absorption band in its infrared spectrum at 3615 cm^{-1} and 3450 cm^{-1}. Its pmr spectrum showed signals at δ 1.86 (s, 3H) for the C-4 methyl protons, and the rest of the protons as a multiplet at δ 1.2-3.80, and its mass spectrum gave a molecular ion peak at 364.102 for $C_{16}H_{28}OS_4$. Attempts at tosylation of the mercapto and hydroxy groups with two equivalents of p-toluenesulfonyl chloride in pyridine afforded a complex inseparable mixture of products. In view of the low yield of 162 it became obvious that very low yield of 131 would be obtained from 162 by this approach and it was thought that protection of the mercapto group would lead to a better yield of the p-toluenesulfonate. Unfortunately however treatment of 162 with one equivalent of sodium hydride

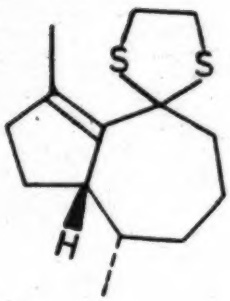
followed by addition of benzyl chloride also gave a mixture of products from which only 20% yield of the S-benzylated product 171 could be isolated. Its infrared spectrum showed an ester carbonyl absorption at 1725 cm^{-1} while its pmr spectrum was clearly diagnostic of the structure. It showed resonance absorption at δ 7.34 (s, 5H) for the phenyl protons, δ 3.3 (s, 2H) for the benzylic methylene proton, δ 3.2-3.4 (m, 4H) for the (-S-CH_2-CH_2-S-) open chain methylene protons, δ 2.6-2.8 (m, 4H) for the thioketal methylene protons, δ 1.70 (s, 3H) for the C-4 methyl protons and also the protons of the carbocyclic ring. It was clear from these low yields that ultimately converting 162 into 131 would not make any substantial difference to the overall yield of 131 from 126, therefore further transformations of 162 into 131 was not investigated.

With the successful synthesis of the key intermediate compounds 131 and 132 which have the correct relative stereochemistry at the C-1, C-10 centres with respect to zierone and epi-zierone respectively, we have solved the stereochemical problem involved in the total synthesis of zierone. We have also introduced the two methyl substituents as well as the C-4, C-5 double bond in zierone and what remained to be done was, in principle, the transposition of the keto-functionality from the C-6 to C-7 position and the introduction of the three-carbon isopropylidene unit into the C-6 position. This ultimate objective could be achieved via the route shown in scheme V, in which the isopropylidene moiety

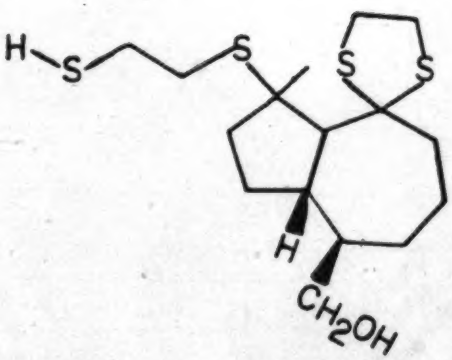
was introduced prior to the formation of the C-7 ketone functionality or by the route shown in scheme VII in which the ketone transposition was accomplished and masked as its dithiane prior to the introduction of the isopropylidene moiety. Both approaches to the synthesis of zierone were investigated. In order to introduce the remaining three-carbon units needed to complete the zierone hydrocarbon skeleton, as per scheme V, 131 was treated with ethynyl magnesium bromide[60] in diethyl ether and also in tetrahydrofuran. In both solvents the desired product 140 was formed in less than 5% yield, the remaining 95% was recovered as starting material 131. When 131 was treated with lithium acetylide ethylenediamine complex[61] in tetrahydrofuran, there was no reaction at temperatures below 25°C, however upon heating the reaction mixture to 35°C it afforded 140 in 10% yield and 173 in 20% yield. However when 131 was treated with lithium acetylide[62] in tetrahydrofuran at -78°C and the reaction mixture allowed to warm to 20°C in two and one-half hours there was 50% conversion of 131 into products with the formation of 17% of 140 and 33% of 173. In an effort to uptimize the yield of the desired product, 140, the reaction was repeated at various temperatures and we were delighted to find that by keeping the temperature below -30°C for a longer period of time, about two hours, the yield of 140 was increased to 60% and the undesired product 173 was formed in 30% yield. The infrared spectrum of 140 showed a broad hydroxyl absorption at 3610 cm^{-1} and a



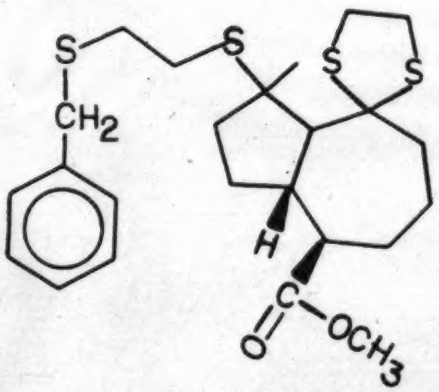
168



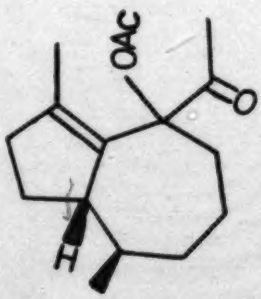
169



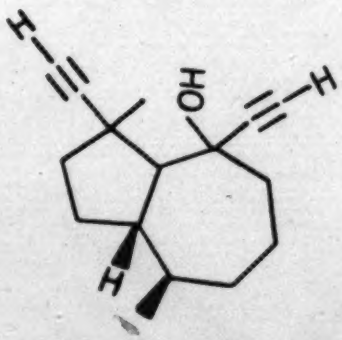
170



171

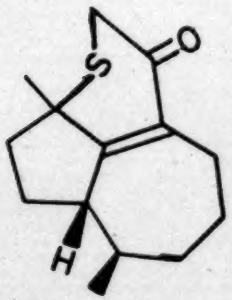


172

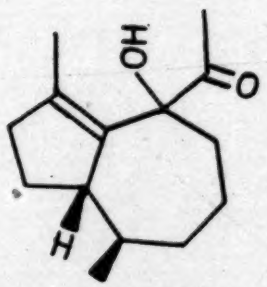


173

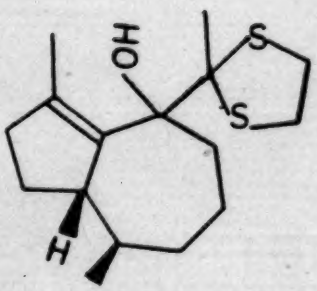
sharp absorption at 3315 cm^{-1} for the acetylenic (-C≡C-H) absorption. Its pmr spectrum showed resonance absorptions at δ 2.00 (s, 3H) for the vinylic methyl protons, δ 2.46 (s, 1H) for the ethynyl (-C≡C-H) proton, δ 0.94 (d, 3H, J = 5 Hz), for the C-10 methyl protons and δ 1.2-3.2 (m, 12H) for the rest of the proton as well as the hydroxyl proton at δ 3.75 (br. s, 1H). The mass spectrum gave a molecular weight of 204.1516 for $C_{14}H_{20}O$ and 186.1409 for the dehydrated molecular ion $C_{14}H_{18}$. The acetylenic functionality was hydrolysed with mercuric acetate in ethyl acetate, followed by reduction of the organo-mercury product to afford the ketoester 172 and the unexpected product 174. When the reduction was effected with hydrogen sulfide[63] gas it afforded 174 in 41% yield and only 25% of the desired product 172. It was thought that hydrogen sulfide, being acidic, was probably catalyzing the addition reaction by protonation of the acetoxy carbonyl group and therefore by using a bulky organic mercaptan addition to the double bond could be minimized, secondly the quantity of the sulfide or mercaptan could be controlled. The organomercury intermediate compound was therefore treated with 2-methyl-2-propanethiol at room temperature for twenty minutes. After purification by column chromatography on silica gel the desired keto-ester was obtained in 48% yield and the undesired product 174 in 30% yield. Repititions of this reaction afforded yields varying from 40% to 55% of the keto-ester 172, indicating the ease of addition of the mercapto group



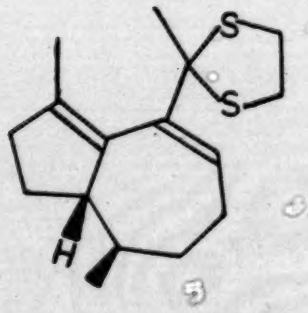
174



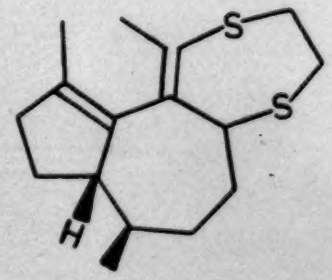
175



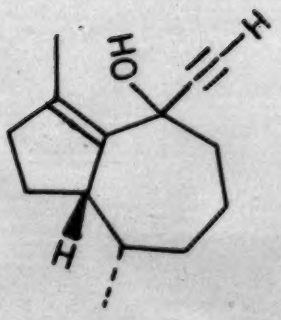
176



177



178



179

to the double bond with the migration of the double bond and elimination of the acetate group. The infrared spectrum of 172 showed carbonyl absorptions at 1735 cm^{-1} for the ester functionality and 1720 cm^{-1} for the ketone group and a carbon-carbon double bond absorption at 1665 cm^{-1}. The pmr spectrum portrayed resonance signals at δ 2.12 (s, 3H) for the acetyl methyl protons, δ 2.06 (s, 3H) for the acetoxy methyl protons δ 1.25 (s, 3H) for the C-4, vinylic methyl protons, δ 0.85 (d, 3H, J = 3 Hz) for the C-10 methyl protons and δ 1.2-3.2 (m, 12H) for the carbocyclic protons. The mass spectrum gave a molecular weight of 264.1737 for $C_{16}H_{24}O_3$ and at 204.1519 corresponding to $C_{14}H_{20}O$ with the loss of acetic acid. The spectra of 174 was also in agreement with the assigned structure. Its infrared spectrum showed a ketone absorption at 1700 cm^{-1} and a carbon-carbon double bond absorption at 1660 cm^{-1}. The proton magnetic resonance portrayed signals at δ 1.10 (s, 3H) for the C-1 methyl protons, δ 2.35 (d, 2H, J = 4 Hz) for the methylene protons between the sulfur and ketone groups, geminally coupled to each other, δ 2.7-3.1 (m, 1H) for the C-1 allylic proton, δ 0.89 (d, 3H, J = 6 Hz) for the C-5 methyl protons and δ 1.2-2.7 (m, 11H) for the carbocyclic protons. The unsaturated ketone 132, the epimer of 131 was also similarly treated with lithium acetylide in tetrahydrofuran to afford the ethynyl compound 179 in 55% yield. The infrared spectrum of 179 showed a hydroxyl absorption at 3600 cm^{-1} and the sharp ethynyl (-C≡C-H) absorption at

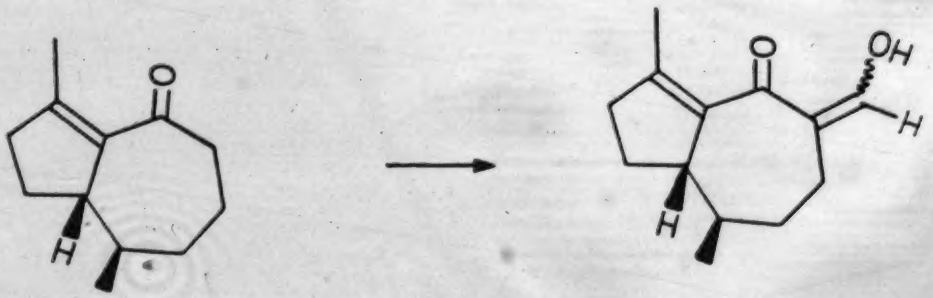
3315 cm^{-1}. The pmr spectrum portrayed signals at δ 2.46 (s, 1H) for the ethynyl (-C≡C-H) proton, δ 1.98 (s, 3H) for the vinylic methyl protons, δ 0.80 (d, 3H, J = 7 Hz) for the C-10 methyl protons. The mass spectrum also gave a molecular weight of 204.1516 for $C_{14}H_{20}O$ and 180.1409 for the dehydrated molecular ion $C_{14}H_{18}$. Upon hydrolysis of the ethynyl moiety with mercuric acetate followed by decomposition of the organo-mercury intermediate compound with 2-methyl-2-propanethiol, 179 afforded 180 in 40% yield and 40% yield of the unsaturated ketone 181. The spectral data of 180 paralleled those of 172. Its infrared spectrum showed absorptions at 1720 cm^{-1} and 1735 cm^{-1} for the ketone and ester carbonyl groups respectively and a carbon-carbon double bond absorption at 1650 cm^{-1}. The pmr spectrum showed resonance peaks at δ 1.24 (s, 3H) for the vinylic methyl protons, δ 2.1 (s, 3H) for the acetyl methyl protons, δ 2.04 (s, 3H) for the acetoxy methyl protons, δ 0.85 (d, 3H, J = 7 Hz) for the C-10 methyl protons. The mass spectrum gave a molecular weight of 264.1737 for $C_{16}H_{24}O_3$ and at 204.1519 corresponding to the molecular ion $C_{14}H_{20}O$ with the loss of acetic acid. The spectral data of 181 was also similar to that of its isomer 174. Its infrared spectrum showed a carbonyl absorption at 1700 cm^{-1} and a carbon-carbon double bond absorption at 1660 cm^{-1}. The pmr spectrum portrayed signals at δ 1.07 (s, 3H) for the C-1 methyl protons, δ 2.35 (d, 2H, J = 3 Hz) for the geminally coupled methylene protons between the sulfur and keto groups,

δ 0.87 (d, 3H, J = 7 Hz) for the C-10 methyl protons and at δ 2.7-3.06 (m, 1H) for the C-1 allylic proton. In order to make the envisaged intermediate dienone 141, the ester functionality of 172 was hydrolyzed with sodium hydroxide in methanol-water mixture to give 175 in 98% isolated yield. The infrared spectrum of 175 showed a broad hydroxyl absorption at 3480 cm^{-1} and a carbon-carbon double bond absorption at 1665 cm^{-1}. The pmr spectrum indicated signals at δ 1.26 (s, 3H) for the vinylic methyl protons, δ 2.1 (s, 3H) for the acetyl methyl protons, δ 0.87 (d, 3H, J = 5 Hz) for the C-10 methyl protons and δ 3.92 (br. s, 1H) for the hydroxyl proton. Unfortunately however, all attempts to dehydrate the hydroxy ketone 175 to give the envisaged dienone intermediate 141 were futile. An inseparable mixture of products was obtained and spectral (pmr and ir) data suggested the presence of only small amounts, (less than 10%) of 141. Consequently the ketone function of 175 was protected as a thioketal by treatment with 1,2-ethanedithiol and catalytic amounts of boron trifluoride etherate to give 176. Preliminary investigation showed that although 176 could be dehydrated to give about 40% of the diene 177, attempts at hydrolysis of the thioketal moiety of 177 were again futile. The rearranged product 178 was the only product isolated. In view of the difficulties encountered in reproducing the results of the formation of 172, coupled with the extremely low yield of 141 from the dehydration of 175 and the rearrangement of 177 to give 178 instead of the

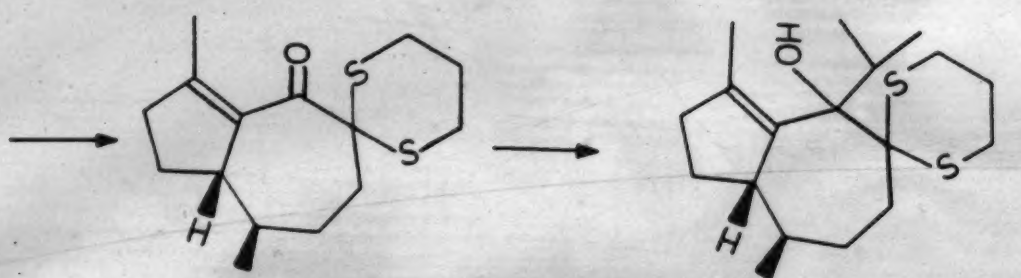
desired dienone 141 it was decided to proceed from 131 via the route proposed in scheme VII as it became obvious that a rather long detour may be required to convert 172 into zierone.

The C-7 position of the unsaturated ketone 131 was functionalized as its 7,7-(propane-1,3-dithio)- derivative by the procedure of Woodward et al.[64] for eventual conversion into the C-7 ketone functionality of zierone. Thus 131 was treated with two equivalents of lithium tert-butoxide and three equivalents of ethyl formate in dimethoxyethane to give the C-7 hydroxymethylene derivative 182 in 67% yield. The infrared spectrum of 182 showed a weak hydroxyl absorption band at 3500 cm^{-1}, presumably due to intramolecular hydrogen bonding and a broad absorption with peak intensity at 1605 cm^{-1} attributed to the dienone system. The proton magnetic resonance spectrum displayed resonance signals at δ 2.01 (s, 3H) for the C-4 vinylic methyl protons, δ 3.2 (br. m, 1H) for the C-1 allylic proton, δ 0.95 (d, 3H, J = 5 Hz) for the C-10 methyl protons, δ 8.27 (d, 1H, J = 5 Hz) for the vinylic proton of the hydroxymethylene group, δ 15.48 (d, J = 5 Hz) (approximately 20%); δ 15.37 (d, J = 5 Hz) (approximately 80%) 1H, for the enolic proton of the hydroxymethylene group and δ 1.2-2.8 (m, 9H) for the remaining carbocyclic protons. The mass spectrum also gave a molecular ion peak at 206.1309 for $C_{13}H_{18}O_2$ corresponding to the proposed formula. The hydroxymethylene derivative was treated with

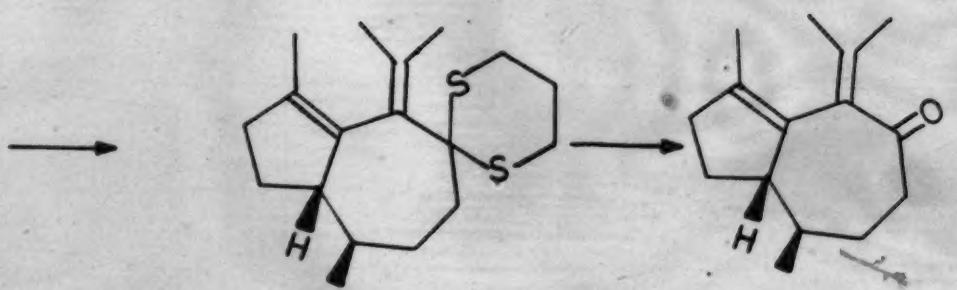
SCHEME VII



131 182



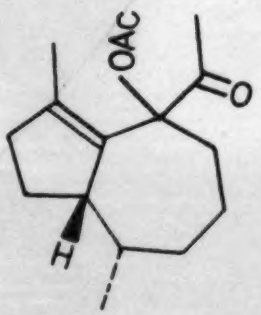
183 184a



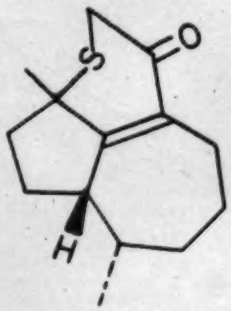
185 1

propane-1,3-dithiol-di-p-toluenesulfonate prepared according to the procedure of Woodward et al.[65] and used accordingly[64] to afford 183 in 44.5% yield after purification by column chromatography on neutral alumina grade I. The infrared spectrum of 183 showed a carbonyl absorption at 1665 cm^{-1} and a carbon-carbon double bond absorption at 1605 cm^{-1}, for the α,β-unsaturated ketone system. The proton magnetic resonance spectrum portrayed signals at δ 2.05 (s, 3H) for the C-4 vinylic methyl protons, δ 0.96 (d, 3H, J = 5 Hz) for the C-10 methyl protons, δ 3.0-3.8 (m, 4H) for the methylene protons bonded directly to the sulfur atoms of the propanedithio- group and δ 1.2-3.0 (m, 14H) for the remaining protons. The mass spectrum gave an intense (45%) molecular ion peak at 282.1108 for $C_{15}H_{22}OS_2$ in agreement with the assigned molecular structure. At this point, what remained to be done was the introduction of the isopropylidene group, followed by hydrolysis of the propane-1,3-dithio- moiety of 185 to afford the target molecule, zierone. An attempt to introduce the remaining three-carbon unit by treatment of 183 with isopropyllithium[66] in diethyl ether yielded disappointing results as a complex mixture of products was obtained. The product mixture was purified by column chromatography on silica gel, followed by further purification by preparative thin layer chromatography on silica gel, but none of the isolated products was the desired product 184a. The identifiable products were found to be 184b, 184c and two others which appeared to be 184d

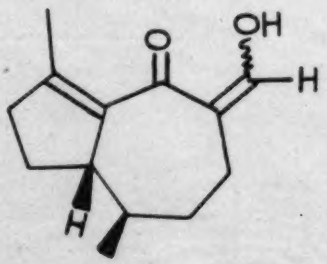
and 184e. The infrared spectrum of 184b showed absorptions at 1600 cm^{-1} and 1665 cm^{-1} for the α,β-unsaturated ketone system, while its pmr spectrum showed resonance signals at δ 2.0, for the vinylic methyl protons, δ 0.86, for the C-10 methyl protons, δ 2.2-3.7, m for the protons adjacent to the sulfur atom (-$\underline{CH}$-S-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-S-$\underline{CH}$-), and at δ 1.3-1.9 for the carbocyclic protons. The infrared spectra of 184c and 184d showed the presence of a saturated carbonyl group with absorption at 1710 cm^{-1}. Their pmr spectra showed the absence of vinylic methyl protons but showed the presence of the isopropyl methyl protons at δ 1.14-1.22, and the presence of the C-4 and C-10 methyl protons at δ 0.85-0.92. It can be seen from these results that the ketone functionally is sterically more hindered and less reactive than the dithiane sulfur atom and the conjugated double bond. In the light of the results obtained from the originally proposed schemes V and VII it may be concluded therefore that, in order to achieve a total synthesis of zierone via the intermediacy of the unsaturated ketone 183, the ketone functionality of 183 would have to be reductively cleaved, followed by hydrolysis of the dithiane moiety to afford the β,γ-unsaturated ketone 183a, which could be converted into zierone by the titanium tetrachloride catalyzed aldol condensation of the silyl enol ether 183b with acetone.[67] This approach seems to be a plausible route left unexplored.



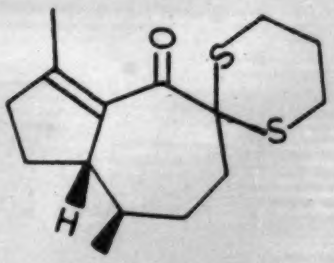
180



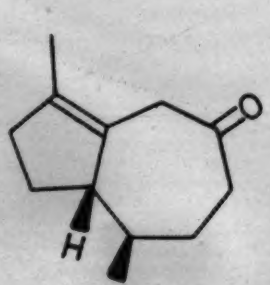
181



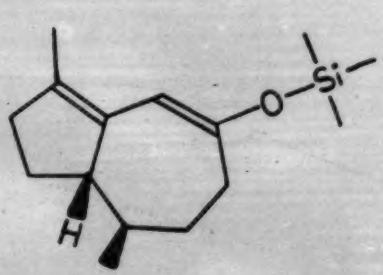
182



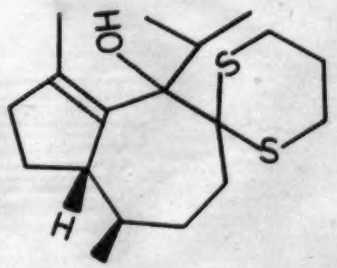
183



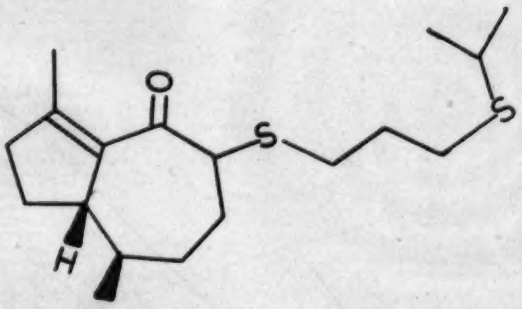
183a



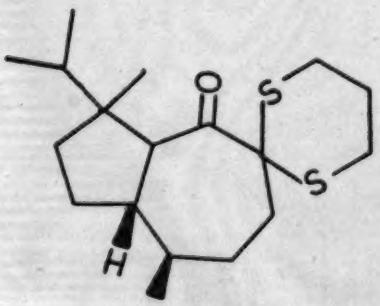
183b



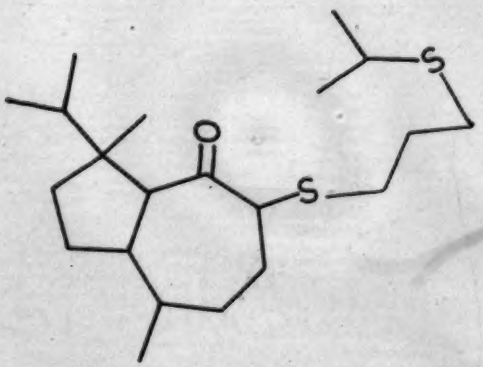
184a



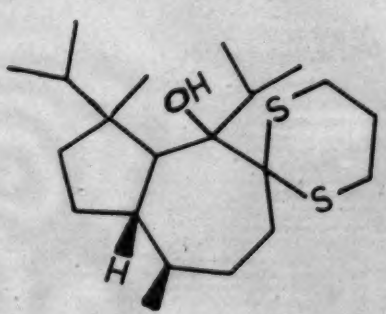
184b



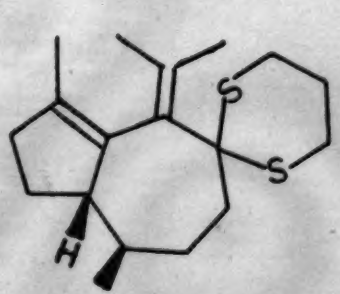
184c



184d



184e



185

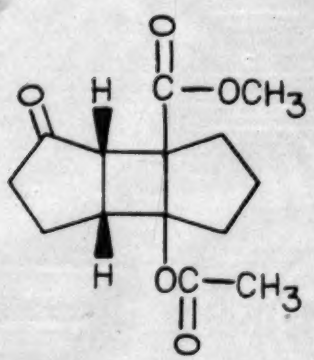
CHAPTER IV: APPROACH TO ZIERONE VIA THE HEAD-TO-TAIL PHOTOCYCLOADDUCTS.

It was shown during the structural and stereochemical elucidation of the photocycloadducts that the head-to-tail photocycloadduct 101 was produced in approximately 50% yield when isopropanol was used as solvent. It was also shown that this keto-diester 101 afforded the lactone-ester 135 in 85% yield upon treatment with methyllithium and that 135 afforded the keto-lactones 136 and 137 in a total of 98% yield upon treatment with sodium methoxide in methanol. It was further shown that the thioketalized photocycloadduct 98 was produced in approximately 11% yield when benzene was used as solvent in the initial photocycloaddition reaction. The thioketal-diester 98 afforded the head-to-tail keto-diester 102 upon hydrolysis of the thioketal moiety with mercuric chloride. When 102 was treated with methyllithium it afforded the hydroxy-diester 134 in 90% yield. The hydroxy-diester 134 also afforded the isomeric keto-lactones 136 and 137 in a total of 98% yield upon treatment with sodium methoxide in methanol. It can be envisaged that the keto-lactones 136 and 137 could be used as intermediates for the synthesis of zierone as shown in scheme VIII. The C-5 ketone functionality can be used to introduce the C-10 methyl group of zierone in a desired orientation in the early stages of the synthesis by taking advantage of the stereochemistry of the lactone functionality. It is anticipated that if the C-10 methyl group of zierone is introduced into 136 via the aldehyde, with an epimerizable centre, the predominant thermodynamically more stable

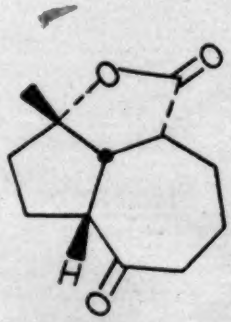
isomer will be the 1,10-Syn product as the 1,10-Anti isomer will have the methyl group or the precursor carboxaldehyde group sterically close to and interacting with the lactone functionality. The lactone carbonyl group can be used to functionalise the C-8 position for eventual introduction of the C-7 keto group of zierone. It can also be used to introduce the remaining two carbon units followed by dehydration to afford the isopropylidene moiety. This approach to the synthesis of zierone was also explored as outlined in scheme VIII.

In persuance of this synthetic scheme, the lactone-ester 135 was treated with 0.2M sodium methoxide in methanol to afford 136 and 137 in a total of 98% yield. The diester 134 was also similarly treated to give 136 and 137 in a total of 98% yield. The structures and stereochemistry of 136 and 137 were assigned from equilibration studies on 136 and 137. When 135 was treated as above for one hour and then quenched with dilute hydrochloric acid, 136 and 137 were obtained in a ratio of 9:1 (136:137). When the reaction was allowed to proceed for two hours the ratio of 136:137 was 4:1 respectively and for four hours this ratio was 1:1. However when the reaction was allowed to proceed longer than four hours a secondary reaction occurred with the formation of the hydroxy-diketone 186. As the C-4, C-12 stereochemistry in the lactone-ester 135 is cis and it is unreasonable to assume that the C-4 centre was rapidly epimerized as soon as the methanolysis-with-fragmentation

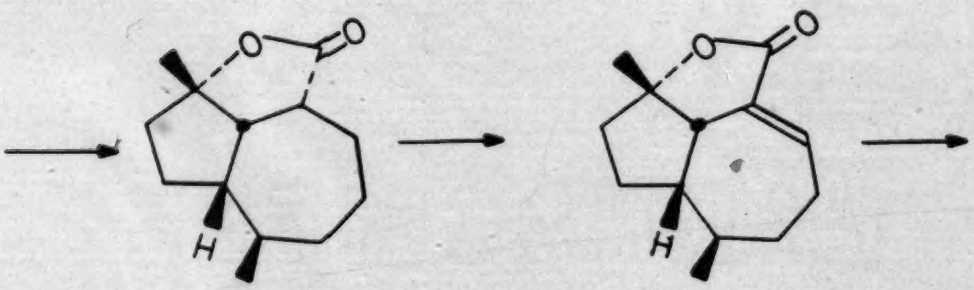
SCHEME VIII



101 OR 102

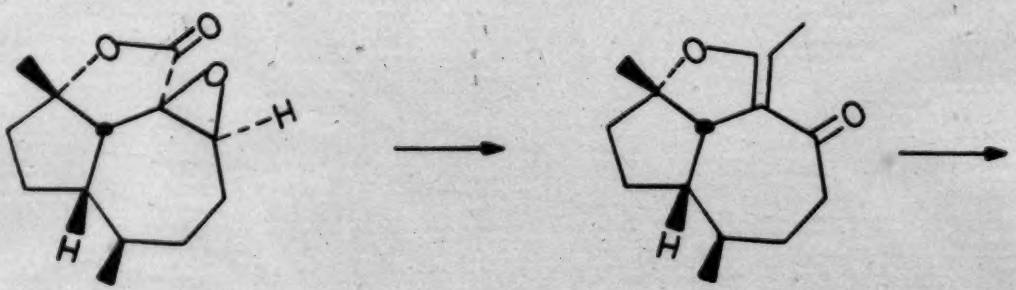


136



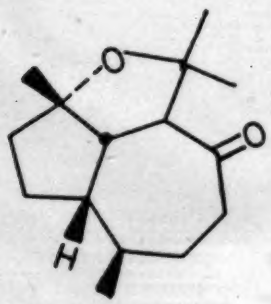
193

219

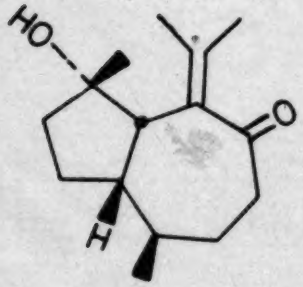


224

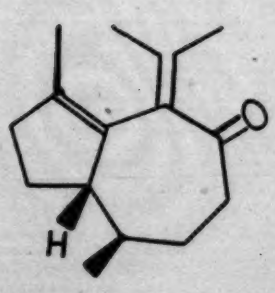
229



230



230a



1

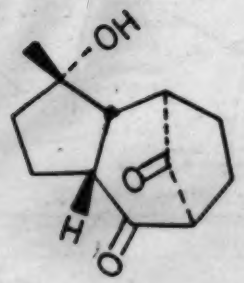
occurred and then it slowly reverted into the original cis relationship with the C-12 centre, the initially formed major isomer was assigned the C-4, C-12, cis ring junction stereochemistry. Secondly the stereochemistry assigned to the C-9 centre in relation to the C-1 centre, the stereochemistry of which has previously been established, was based on the Alder-Stein rules for lactones, which favours the assigned cis stereochemistry. It should be mentioned here that 137 was later shown conclusively to be a C-4 and not a C-9 epimer of 136. The infrared spectrum of the keto-lactone 136 portrayed the cycloheptanone carbonyl absorption at 1700 cm^{-1} and the γ-lactone carbonyl absorption at 1760 cm^{-1}. The proton magnetic resonance spectrum of 136 showed resonance absorptions at δ 1.48 (s, 3H) for the C-1 methyl protons, δ 2.5 (t, 1H, J = 6 Hz), for the C-12 methine proton, δ 3.14 (m, 2H) for the C-4 and C-9 methine protons and δ 1.5-2.7 (m, 10H) for the remaining carbocyclic protons. The mass spectrum gave a molecular ion peak of 98% intensity at 208.1101 for $C_{12}H_{16}O_3$ in agreement with the assigned molecular formula. The spectral data of 137 was similar to that of 136. Its infrared spectrum gave two carbonyl absorptions at 1700 cm^{-1} and 1755 cm^{-1} for the ketone and γ-lactone functional groups respectively while its proton magnetic resonance spectrum indicated signals at δ 1.52 (s, 3H) for the C-1 methyl protons, δ 2.48 (dd, 1H, J = 6 Hz, J' = 10 Hz) for the C-12 methine proton, δ 3.14 (m, 2H) for the C-4 and C-9 methine protons and

δ 1.6-2.4 (m, 10H) for the rest of the carbocyclic protons. The mass spectrum also gave a molecular ion peak at 208.1098 for $C_{12}H_{16}O_3$, thus confirming 136 and 137 to be isomeric. The assigned cis stereochemistry of the lactone moiety of both 136 and 137 is supported by the observed coupling of 6 Hz between the C-9 and C-12 methine protons. The coupling between the C-9 and C-12 protons of 136 is the same as the coupling between the C-4 and C-12 protons. Since the C-4 and C-12 protons have been shown to be cis to each other, the C-9 and C-12 protons can also be inferred to be cis to each other. This is in contrast to the observed coupling of 10 Hz between the C-4 and C-12 protons of 137 which have been shown to be trans to each other. The infrared spectrum of the hydroxy-diketone 186 showed a broad hydroxyl band at 3600 cm^{-1} and two carbonyl absorptions at 1710 cm^{-1} for the cycloheptanone-cyclopentanone keto group and at 1760 cm^{-1} for the cyclopentanone-cyclohexanone ketone functionality, Its proton magnetic resonance spectrum portrayed signals at δ 1.54 (s, 3H) for the C-4 methyl protons, δ 2.88-3.30 (br. s, 4H) for the hydroxyl proton and the C-6, C-8 and C-1 methine protons. The remaining carbocyclic protons appeared at δ 1.8-2.8. It should be mentioned that 186 was converted into 136 when it was heated under reflux with p-toluene-sulfonic acid in benzene for four hours.

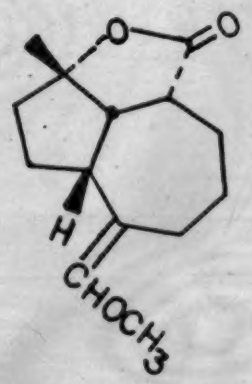
As already pointed out the high yields of 136 and 137 made them very attractive as intermediate compounds in the synthesis of zierone. In order to convert the C-5 keto

group of 136 into a C-10 methyl group of zierone the keto-lactone 136 was added to a solution of methoxymethylene-triphenylphosphorane in tetrahydrofuran to afford the methyl vinyl ether in 80% yield as an isomeric mixture. Column chromatography of the mixture on silica gel afforded a major isomer 187 in 52% yield and a second fraction (fraction B). The infrared spectrum of the major isomer showed a γ-lactone carbonyl absorption at 1760 cm^{-1} and carbon-carbon double bond absorption at 1675 cm^{-1}. Its proton magnetic resonance spectrum indicated resonance signals at δ 5.65 (s, 1H) for the vinylic proton, δ 3.50 (s, 3H) for the methoxy methyl protons. δ 3.4 (m, 2H) for the C-4 and C-9 methine protons. δ 1.40 (s, 3H) for the C-4 methyl protons and δ 1.4-2.6 (m, 11H) for the remaining carbocyclic protons. The mass spectrum gave a molecular ion peak as its base peak at 236.1411 corresponding to the expected molecular formula of $C_{14}H_{20}O_3$. Pmr analysis of the second fraction (fraction B) showed it to contain an isomeric mixture of methyl vinyl ethers. The vinyl ether 187 was hydrolysed by treatment with 6M hydrochloric acid in tetrahydrofuran-water mixture at room temperature for four hours to give a single aldehyde 189 in 100% yield. It is interesting to note that while the major vinyl ether 187 afforded only one aldehyde 189, hydrolysis of the second fraction (fraction B) afforded two aldehydes, one of which obtained in 13% yield was identical with 189. The other aldehyde 190 produced in 16% yield was thought to arise from 137 which was formed by epimerization of 136 at the C-4

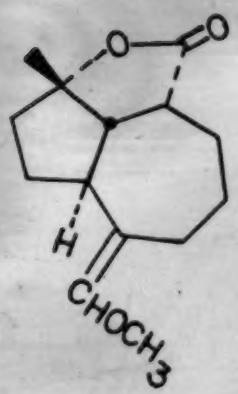
centre under the reaction conditions. Thus the total ratio of 187:188 was 5:1 respectively. This was indeed found to be the case for when 137 was similarly treated with methoxymethylene triphenylphosphorane it afforded an inseparable mixture of vinyl ethers in about 80% yield. Hydrolysis of this vinyl ether mixture with 6M hydrochloric acid in tetrahydrofuran-water mixture afforded two aldehydes which were found to be identical with 189 and 190 in a ratio of 1:5 (189:190) in a total of 100% yield. The infrared spectrum of the aldehyde 189 showed two carbonyl absorptions at 1730 cm^{-1} for the aldehydic group and at 1755 cm^{-1} for the γ-lactone group. Its proton magnetic resonance spectrum showed prominent resonance signals at δ 1.48 (s, 3H) for the C-1 methyl protons and at δ 9.50 (br. s, 1H) for the aldehydic proton. The infrared spectrum of 190 also showed two carbonyl absorptions at 1730 cm^{-1} and 1755 cm^{-1} for the aldehyde and γ-lactone functional groups respectively. The pmr spectrum showed two prominent signals at δ 1.51 (s, 3H) for the C-1 methyl protons and δ 9.58 (br. s, 1H) for the aldehydic proton. The mass spectra of both compounds gave a molecular ion peak at 222.1253 for $C_{13}H_{18}O_3$ in agreement with the expected molecula formulae. The aldehydes 189 and 190 were converted into their respective thioketals 191 and 192 by treatment with 1,2-ethanedithiol and catalytic amount of boron trifluoride etherate, followed by column chromatographic purification on silica gel. In view of the observation that the keto-lactones 136 and 137 afforded the same



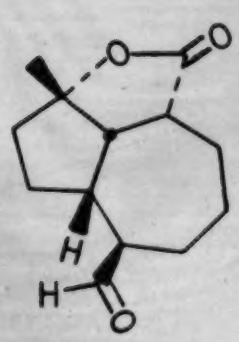
186



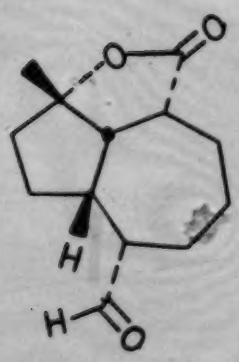
187



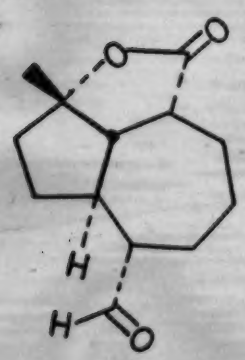
188



189



189a

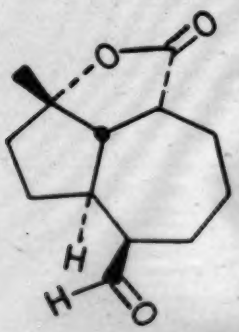


190

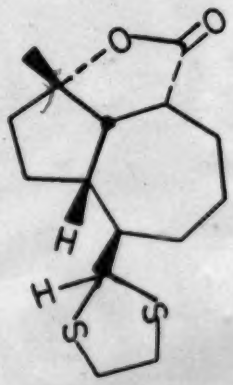
mixtures of intermediate products these were separated at the thioketal stage in subsequent reactions since the thioketals were found to be more stable than the corresponding aldehydes and easier to separate as compared to the keto-lactones 136 and 137.

The spectral data of these thioketals were in agreement with the assigned structures. The infrared spectrum of the thioketal-lactone 191 showed a strong γ-lactone carbonyl absorption at 1750 cm^{-1} while its protons resonated at δ 4.84 (d, 1H, J = 2 Hz) for the dithiomethyl proton, δ 3.16 (s, 4H) for the thioketal methylene protons (-S-CH_2-CH_2-S-) δ 1.40 (s, 3H) for the C-1 methyl protons in addition to the signals of the remaining carbocyclic protons. The mass spectrum of 191 also gave a molecular ion peak as its base peak at 298.1061 for the molecular formula $C_{15}H_{22}O_2S_2$. The infrared spectrum of 192 also showed a γ-lactone carbonyl absorption at 1755 cm^{-1} while its pmr spectrum displayed signals at δ 4.76 (d, 1H, J = 3 Hz) for the dithiomethyl proton, δ 3.2 (m, 4H) for the thioketal methylene protons, δ 1.46 (s, 3H) for the C-1 methyl protons and δ 1.2-2.8 (m, 14H) for the carbocyclic protons. The mass spectrum also gave a molecular ion peak at 298.1061 corresponding to the calculated molecular weight for the formula of $C_{15}H_{22}O_2S_2$. In order to obtain the C-5 methyl group of the hydroazulene skeleton the thioketals 191 and 192 were reductively cleaved with Raney nickel (W-2) in benzene to afford the C-5 methyl derivatives 193 and 194

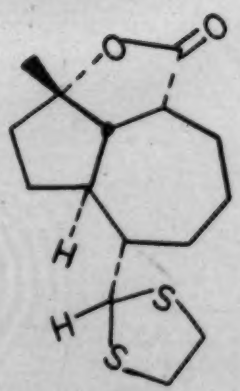
respectively in 85% yield each. The infrared spectrum of 193 gave a γ-lactone carbonyl absorption at 1750 cm^{-1}. Its pmr spectrum portrayed signals at δ 0.89 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.37 (s, 3H) for the C-1 methyl protons, δ 2.48 (t, 1H, J = 6 Hz) for the C-12 methine proton, δ 2.90 (m, 1H) for the C-9 methine proton, and δ 1.1-2.5 (m, 12H) for the remaining carbocyclic protons. The mass spectrum gave a molecular ion peak at 208.1469 for $C_{13}H_{20}O_2$ in support of the molecular formula. The infrared spectrum of the isomeric lactone 194 also showed a γ-lactone carbonyl absorption at 1750 cm^{-1} while its pmr spectrum showed resonance peaks at δ 0.95 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.40 (s, 3H) for the C-1 methyl protons and at δ 1.2-2.6 (m, 14H) for the remaining carbocyclic protons. Its mass spectrum also gave a molecular ion peak at 208.1469 corresponding to the assigned molecular structure. The formation of only two isomers out of the four possible isomers, 193, 194, 195 and 196 arising from the C-4 and C-5 chiral centres is interesting. The formation of only one aldehyde, 189, produced under equilibrating conditions from 187 suggested that the thermodynamically more stable 1,10-syn [C-4 H syn to C-5 methyl] was formed. This isomer was considered more stable than the 1,10-anti isomer 189a which would have led to 195, as the carboxy-aldehyde group of 189a would lie close to the lactone functionality leading to severe steric interactions. This same rationale holds true for the thioketal subsequently prepared



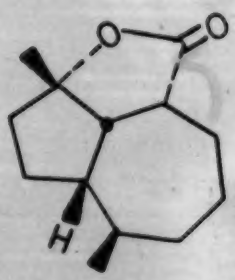
190a



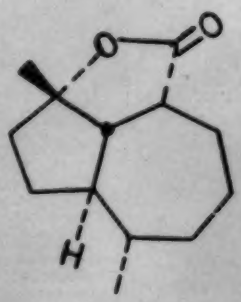
191



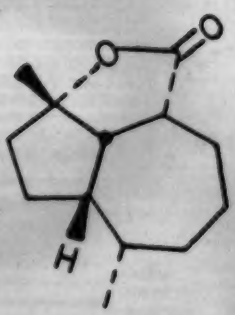
192



193



194



195

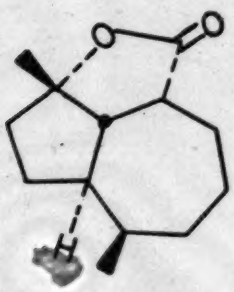
from 189, hence the assignment of the stereochemistry of 193 and its precursors as such.

As mentioned earlier, the second chromatography fraction, (fraction B) which contained a mixture of vinyl ethers afforded two aldehydes which were separately converted into 193 and 194. It should also be recalled that the keto-lactone 137 also afforded two aldehydes via the vinyl ethers which were also converted into 193 and 194 in a ratio of 1:5. In summary therefore it was found that 136 afforded 193 and 194 in a ratio of 1:5 respectively. The formation of the C-10 methyl derivatives in these respective ratios led to the conclusion that the major product 193 obtained from 136 was formed with retention of the C-4, C-12 cis ring junction stereochemistry, while the minor product arose from the C-4 epimerized centre. Similarly the major product 194 obtained from 137 was formed with retention of the C-4, C-12 trans ring junction stereochemistry while the minor product arose from the C-4 epimerized centre. The assignment of the stereochemistry of 194 and consequently its precursor aldehyde and thioketal was based on the chemical shift of its C-5 methyl protons compared to that of 193. It was reasoned that the methyl group was on the same face of the molecule as the lactone functionality and was therefore deshielded by the lactone carbonyl group. The steric interaction that the precursor aldehyde 190 and its thioketal derivative 192 could encounter is minimal compared to those of 189a and its thioketal derivative due to the trans

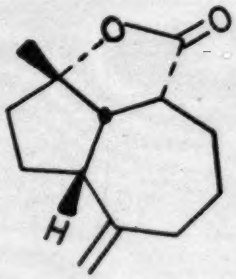
relationship of the fused ring junction allowing more flexible conformational mobility to accommodate the C-5 carboxyaldehyde and thioketal groups and consequently the C-5 methyl group of 194. It can therefore be seen here that the stereochemistry of the lactone functionality has been utilized to control the introduction of the C-5 methyl group such that only the desired 1,10-syn isomer with respect to the assigned stereochemistry of zierone was formed. The stereochemistry of the C-9 centre was presumed to have been retained in these chemical transformations as a direct consequence of the Alder Stein rule for lactones, and is supported by the observed coupling between the C-9 and C-12 protons (J = 6 Hz).

As one of the objectives in the synthesis of zierone was to unambiguously prove its stereochemistry or otherwise, it was thought necessary to confirm the assigned stereochemistry of 193 and 194 which have been based on theoretical considerations. Consequently the keto-lactone 136 which could be obtained from 135 in 90% yield was added to a solution of methylenetriphenylphosphorane in tetrahydrofuran to afford the methylene derivative 197 in 60% yield as the only product. The absence of any C-1 epimeric methylene compound in this case could be attributed to the higher reactivity of the latter phosphorane with the ketone. The infrared spectrum of 197 showed the γ-lactone carbonyl absorption at 1755 cm^{-1} and a carbon-carbon double bond absorption at 1650 cm^{-1}. Its proton magnetic resonance

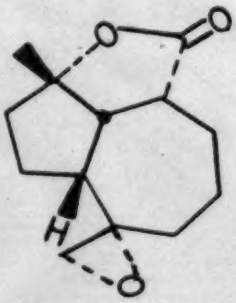
spectrum portrayed resonances at δ 4.64 (d, 2H, J < 1 Hz) for the vinylic methylene protons and δ 1.40 (s, 3H) for the C-1 methyl protons. Its mass spectrum also gave a molecular ion peak as its base peak at 206.1307 for the assigned molecular formula of $C_{13}H_{18}O_2$. Upon treatment with m-chloroperbenzoic acid, 197 afforded two oxiranes 198 and 199 in 98% yield in a ratio of 1:1.5 respectively. The assignment of the stereochemistry of these two epoxides was based on the chemical shifts of the protons of the methylene groups of the epoxides. The methylene protons of the β-epoxide 199 was thought to be deshielded by the lactone carbonyl group compared to those of the α-epoxide 198. However these assignments are not crucial to the current stereochemical elucidation. The infrared spectrum of 198 showed a γ-lactone carbonyl absorption at 1755 cm^{-1} while its pmr spectrum showed signals at δ 1.42 (s, 3H) for the C-1 methyl protons, δ 2.45 (d, 1H, J = 5 Hz) and δ 2.76 (1H), for the oxirane methylene protons. The infrared spectrum of 199 also gave a γ-lactone carbonyl absorption at 1755 cm^{-1} and its pmr spectrum showed resonance peaks at δ 1.42 (s, 3H) for the C-1 methyl protons, δ 2.57 (d, 1H, J = 5 Hz) and δ 2.76 (d, 1H, J = 5 Hz) for the oxirane methylene protons. The mass spectrum of both compounds gave a molecular ion peak at 222.1258 for $C_{13}H_{18}O_3$. Both epoxides were independently treated with boron trifluoride etherate in benzene and rearranged to give the same single aldehyde 200 which was found to be identical with 189. When both



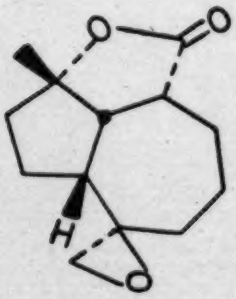
196



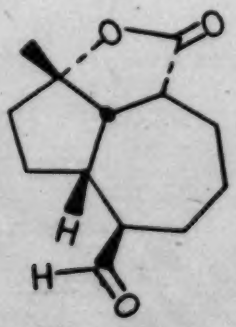
197



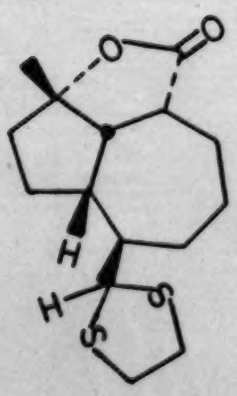
198



199



200



201

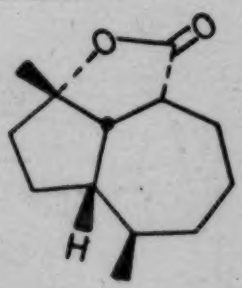
aldehydes were separately treated with 1,2-ethanedithiol and boron trifluoride etherate they afforded the same single thioketal, 201 [ir 1750 cm^{-1}, pmr, δ 4.84 (d, 1H, J = 2 Hz), δ 3.16 (s, 4H), δ 1.40 (s, 3H) m/e 298.1061 for $C_{15}H_{22}O_2S_2$] which was found to be identical with 191. furthermore when 201 was treated with Raney nickel (w-2) it afforded the C-5 methyl derivative 202 which was found to be identical with 193 in all respects. [ir 1750 cm^{-1}; pmr, δ 0.89 (d, 3H, J = 5 Hz), δ 1.37 (s, 3H), δ 2.48 (t, 1H, J = 6 Hz), δ 2.90 (m, 1H), δ 1.1-2.5 (m, 12H); m/e 208.1469 for $C_{13}H_{20}O_2$]. It was thought that hydrogenation of the C-10 methylene compound 197 would result in the formation of 195 as a major product as hydrogenation was expected to occur from the sterically less hindered β-face of the molecule. However upon hydrogenation in ethyl acetate using palladium on carbon as catalyst at one atmosphere an inseparable mixture of products was obtained. Proton magnetic resonance spectral analysis of this mixture showed the presence of two major isomers constituting about 70% of the product mixture in a ratio of 3:2. The major product with a C-1 methyl chemical shift at δ 1.37 was assigned the structure of 193. The other product with a C-1 methyl chemical shift at δ 1.25 was assigned the structure of 195. The remaining two minor compounds with C-1 methyl chemical shifts at δ 1.44 and 1.40 were assigned the structures of 194 and 196 respectively and were considered to have arisen from isomerization of the exocyclic double bond prior to

hydrogenation. Although these results did not prove the assigned stereochemistry of these compounds it supported the idea that the lactones 193 and 194 differed at the C-4 centre. It is however important to note that both epoxides 198 and 199 gave the same single aldehyde under equilibrating conditions. Whether the isomerization of the epoxides proceeded via the hydride shift mechanism or enol type mechanism the reaction conditions were such that the aldehyde could epimerize via the enol. Since the epoxides 198 and 199 and the methyl vinyl ether 187 proceed via similar enol type intermediates towards the ultimate formation of 193 it was concluded finally that the second isomer produced in the hydrolysis of the second chromatography fraction (fraction B) was the C-4 epimer. This result also supported the idea that the thermodynamically more stable aldehyde was formed from both the hydrolysis of the vinyl ether and the rearrangement of the epoxides. All of the above results however did not conclusively prove the assigned stereochemistry of the lactones 193 and 194 and it was necessary to further eleborate on the structures of 193 and 194 to prove their stereochemistry. As the stereochemistry of the C-4 centres in both 193 and 194 have been unequivocally established it was envisaged that by converting 193 and 194 into either of the isomeric enones 131 (1,10-syn) or 132 (1,10-anti), the structure and stereochemistry of which have been unequivocally established, the stereochemistry of 193 and 194 would be conclusively

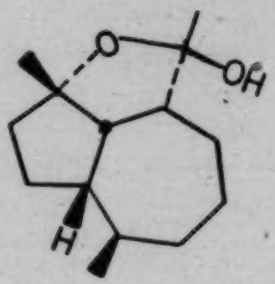
proven.

In this connection the lactone 193 was treated with methylmagnesium bromide in diethyl ether followed by acidification with dilute hydrochloric acid and isolation of products to afford the dehydrated derivative 204 instead of the alcohol 203. The infrared spectrum of the product showed the absence of a hydroxyl group absorption but showed a weak carbon-carbon double bond absorption at 1700 cm^{-1}. Its pmr spectrum showed resonance signals at δ 0.91 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.18 (s, 3H) for the C-1 methyl protons, δ 1.20 (s, 3H) for the vinylic methyl protons, δ 3.1-3.7 (m, 1H) for the allylic methine proton and δ 1.2-2.7 (m, 12H) for the remaining carbocyclic protons. Its mass spectrum also gave a molecular ion peak of 80% intensity at 206.1673 in agreement with the molecular formula of $C_{14}H_{22}O$. Ozonolysis of 204 followed by decomposition of the intermediate ozonide with methyl sulfide afforded the keto-ester 205, the infrared spectrum of which showed two carbonyl absorptions at 1705 cm^{-1} for the cycloheptanone carbonyl and at 1725 cm^{-1} for the ester carbonyl groups. The pmr spectrum clearly showed three methyl signals at δ 0.99 (d, 3H, J = 5 Hz) for the C-10 methyl protons, δ 1.67 (s, 3H) for the C-4 methyl protons and δ 1.9 (s, 3H) for the acetoxy methyl protons. Its mass spectrum gave a molecular ion peak at 238.1569 for $C_{14}H_{22}O_3$ and at 178.1359 for $C_{12}H_{18}O$ with the loss of acetic acid. When the keto-ester 205 was treated with methanolic sodium

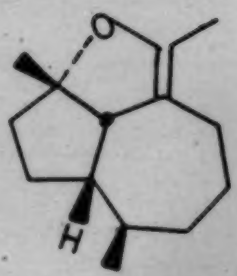
methoxide it afforded the α,β-unsaturated ketone 206. Its infrared spectrum showed an intense carbonyl absorption at 1680 cm^{-1} and a strong absorption due to the carbon-carbon double bond in conjugation with the ketone functionality at 1610 cm^{-1}. The pmr spectrum showed resonance signals at δ 2.02 (s, 3H) for the vinylic methyl protons, δ 0.96 (d, 3H, J = 5 Hz) for the C-10 methyl protons and at δ 1.2-2.7 (m, 12H) for the carbocyclic protons. The mass spectrum gave a molecular ion peak at 178.1359 in agreement with the assigned molecular formula $C_{12}H_{18}O$. The spectral data of 206 showed clearly that it is identical with 131. Therefore the formation of 206 (131) from 193 conclusively proved that the stereochemistry of 193 was infact correctly assigned. It also proved the stereochemistry of the C-4, C-5 centres of the precursors of 193. The isomeric lactone 194 was also treated with methyllithium en route to 131 or 132, affording the alcohol 207. Although the alcohol was stable as a solid it slowly underwent dehydration in solution to give 208. Consequently 207 was treated with camphorsulfonic acid in benzene to afford 208. Its pmr spectrum showed signals at δ 0.93 (d, J = 5 Hz, 3H) for the C-5 methyl protons, δ 1.70 (s, 3H) for the vinylic methyl protons δ 1.30 (s, 3H) for the C-1 methyl protons and at δ 2.70 (d, 1H, J = 8 Hz) for the C-12 methine proton. Ozonolysis of 208 followed by decomposition of the ozonide with methyl sulfide afforded the keto-ester 209. Its infrared spectrum gave two carbonyl absorptions at 1705 cm^{-1} and 1725 cm^{-1} for the



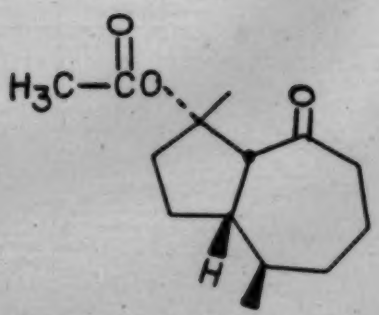
202



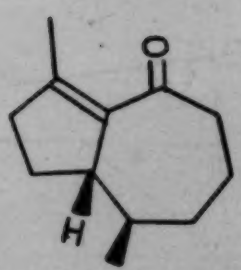
203



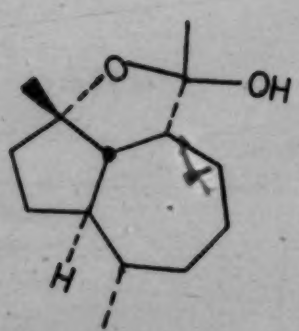
204



205



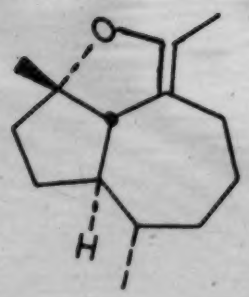
206



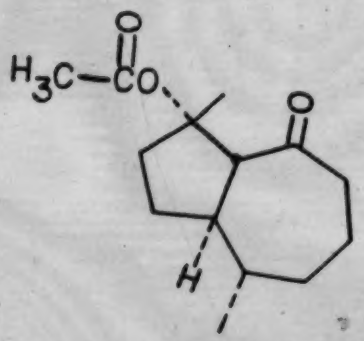
207

ketone and ester functionalities respectively while its pmr spectrum gave resonance signals at δ 0.95 (3H) for the C-10 methyl protons, δ 1.93 (s, 3H) for the acetoxy methyl protons, δ 1.44 (s, 3H) for the C-4 methyl protons and δ 3.65 (d, 1H, J = 8 Hz) for the C-5 methine proton. When the keto-ester 209 was treated with sodium methoxide in methanol it afforded the enone 210, the infrared spectrum of which showed absorption bands at 1680 cm^{-1} and 1610 cm^{-1} for the ketone group and the carbon-carbon double bond respectively, while its pmr spectrum showed resonance peaks at δ 0.96 (d, 3H, J = 5 Hz) for the C-10 methyl protons, δ 2.02 (s, 3H) for the vinylic methyl protons and δ 1.2-2.7 (m, 12H) for the remaining carbocyclic protons. The mass spectrum gave a molecular ion peak at 178.1359 for $C_{12}H_{18}O$. These results showed that 210 was identical with 206 and 131. The results also proved finally that 137 is a C-4 epimer of 136, for, if it was not the C-4 epimer, the corresponding C-5 epimer of 193, that is 195, would have been formed and this would have led to the enone 132 from the above transformations. They also proved conclusively that the assigned 1,10-syn stereochemistry of 194 was correct as the 1,10-anti isomer 196 would have produced 132. At this point it can be said that the stereochemical problem involved in the synthesis of zierone along scheme VIII has been solved as the C-9 chiral centre of 193 and 194 would eventually be destroyed.

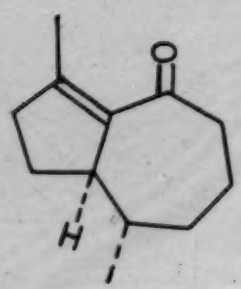
In summary, the intermediate lactones 193 and 194 which



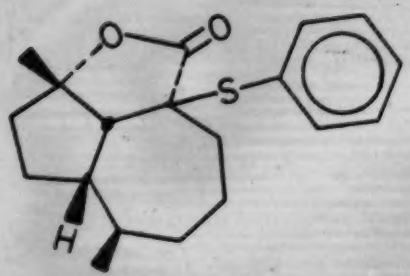
208



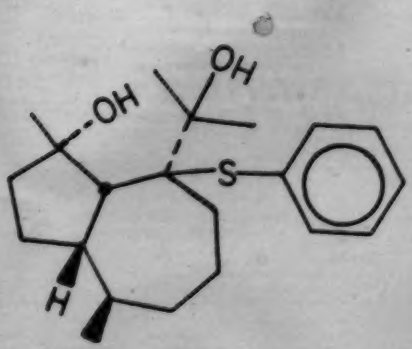
209



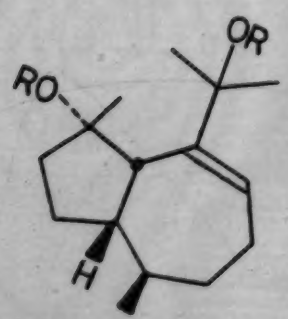
210



211



212



213

contain the C-5 methyl group syn to the C-4 proton were prepared from the head-to-tail photoadducts 101 and 102 by the treatment of these keto-diesters 101 and 102 with methyllithium followed by treatment of the resulting products with sodium methoxide to give the keto-lactones 136 and 137. The keto-lactones were converted into the methyl vinyl ethers 187 and 188 which were hydrolysed to give two aldehydes 189 and 190. The aldehydes were thioketalized with 1,2-ethanedithiol to give the corresponding thioketals 191 and 192. Reductive cleavage of the thioketals with Raney nickel (W-2) then afforded 193 and 194. The stereochemistry of the C-5 methyl group has also been shown to be syn to the C-4 proton in both compounds, that is the same stereochemistry of the C-10 and C-1 centres of the target molecule zierone.

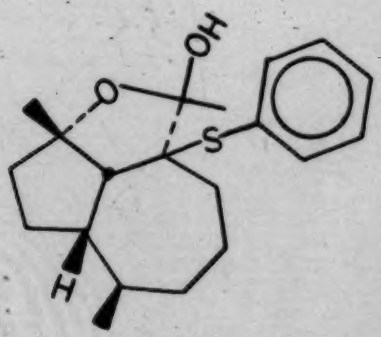
As already mentioned, the lactone carbonyl was thought to be useful for the introduction of the remaining two carbon units and for the functionatization of the C-8 position for its eventual conversion into the ketone function of zierone. Some preliminary exploratory work was done on 193 by converting it into the α-phenylthio derivative with the objective of introducing the geminal dimethyl group followed by elimination of ~~phenylsulfinic~~ benzenesulfenic acid to introduce the C-8, C-9 double bond, thereby forming a compound of type 213, as elimination of the ~~phenylsulfinic~~ benzenesulfenic acid is known to occur via syn elimination and also to be kinetic controlled, hence the expected formation of the least substituted

olefin.[68] The lactone 193 was therefore treated with lithium diisopropylamide and then diphenyldisulfide in tetrahydrofuran to afford the α-phenylthio derivative 211 in 75% yield. Its infrared spectrum showed significantly the γ-lactone carbonyl absorption at 1750 cm^{-1}. The pmr spectrum showed resonance signals at δ 7.2-7.5 (m, 5H) for the aromatic protons, δ 1.68 (d, 3H) for the C-1 methyl protons, δ 0.89 (d, 3H, J = 5 Hz) for the C-5 methyl protons, while the mass spectrum gave a molecular ion peak of 85.60% intensity at 316.1502 for $C_{19}H_{24}O_2S$ in agreement with the expected molecular formula. When 211 was treated with excess methyllithium it failed to give the desired diol 212, instead it gave an epimeric mixture of the hemiketal 214 in 95% yield. The infrared spectrum of 214 showed the hydroxyl absorption bands at 3605 cm^{-1} and 3410 cm^{-1}. The pmr spectrum showed that it consisted of two hemiketals with resonance absorption signals at δ 0.8 (3H) for the C-5 methyl protons, δ 1.3 (s, 3H) for the C-1 methyl protons, δ 1.20 (s, 3H) for the remaining methyl protons, δ 3.32; δ 3.35 (1H) for the hydroxyl proton and δ 7.1-7.45 (m, 5H) for the aromatic protons. The mass spectrum gave a molecular ion peak of 50.23% intensity at 332.2707 corresponding to the assigned molecular formula of $C_{20}H_{26}O_2S$. Although the hemiketal 214 could be isolated and identified it slowly decomposed into a mixture of products. It was therefore treated with sodium hydride and then methyl iodide in tetrahydrofuran to afford a single ketal 215 in 98% yield,

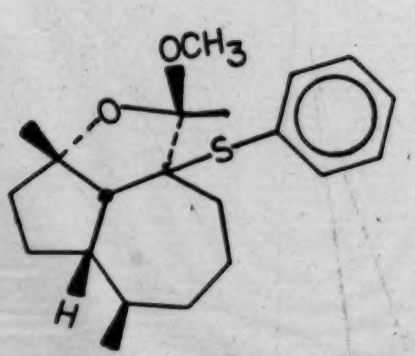
indicating that the hemiketal epimerized prior to kinetic methylation of the alkoxide from the less hindered side of the molecule. The infrared spectrum of 215 was not valuable as a diagnostic tool, however the proton magnetic resonance spectrum displayed resonance signals at δ 0.89 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.2 (s, 3H) for the C-1 methyl protons, δ 3.32 (s, 3H) for the methoxy methyl protons, δ 1.54 (s, 3H) for the remaining methyl protons, and δ 7.1-7.2 (m, 3H); δ 7.4-7.6 (m, 2H) for the aromatic protons. The mass spectrum gave a low intensity molecular ion peak at 346.1973 for $C_{21}H_{30}O_2S$. In view of the fact that the desired diol 212 was not formed from 211, the pursuit of 213 was discontinued.

It was reasoned that since the elimination of phenylselenic acid is known to occur at 0°C or at room temperature[69] as compared to the elimination of phenylsulfinic acid which occurs at much higher temperatures, the α-phenylseleno derivative 216 would serve as a better precursor of the unsaturated lactone 219 than the corresponding α-phenylthio derivative 211. The lactone 193 was therefore added to lithium diisopropylamide followed by addition of phenyseleninyl chloride in tetrahydrofuran at -78°C to afford the α-phenylseleneno-lactone 216 in 85% yield after purification by column chromatography on silica gel. The infrared spectrum of 216 showed a γ-lactone carbonyl absorption at 1750 cm^{-1} while its pmr spectrum showed resonance signals at δ 0.87 (d, 3H, J = 5 Hz) for the C-5

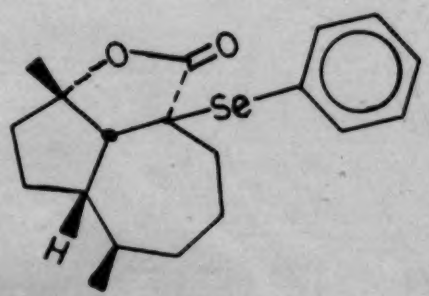
methyl protons, δ 1.64 (s, 3H) for the C-1 methyl protons, deshielded by the aromatic ring, and δ 7.55 (d, 1H, J = 2 Hz); δ 7.48 (d, 2H, J = 2 Hz); δ 7.1-7.38 (3H) for the aromatic protons. The mass spectrum was also in agreement with the calculated molecular formula by showing a molecular ion peak of 41% intensity at 364.0954 corresponding to $C_{19}H_{24}O_2Se$. The isomeric lactone 194 was also similarly converted into its α-phenylseleneno-derivative 217 in 80% yield. The infrared spectrum of 217 showed a γ-lactone carbonyl absorption at 1750 cm^{-1} while its pmr spectrum portrayed signals at δ 1.1 (d, 3H, J = 5 Hz) for the C-5 methyl protons deshielded by the lactone carbonyl group as compared to the resonance frequency of the C-5 methyl protons of 216, δ 1.52 (s, 3H) for the C-1 methyl protons, δ 2.4 (d, 1H, J = 14 Hz) for the C-12 methine proton, trans and coupled to the C-4 proton, and δ 7.6 (d, 1H, J = 2 Hz); δ 7.53 (d, 1H, J = 2 Hz); δ 7.2-7.45 (3H) for the aromatic protons. Its mass spectrum also gave a molecular ion peak of 39.46% intensity at 364.0941 for $C_{19}H_{24}O_2Se$. When 216 was treated with hydrogen peroxide in methylene chloride at 0°C and the reaction mixture allowed to warm to room temperature the unsaturated lactone 219 was obtained in 98% yield via the formation of α-phenylselenoxide followed by an in situ elimination of phenylselenic acid. The α-phenylseleno-lactone 217 was similarly converted into the corresponding unsaturated lactone 220 in 90% yield. The infrared spectrum of 219 showed an α,β-unsaturated γ-lactone carbonyl



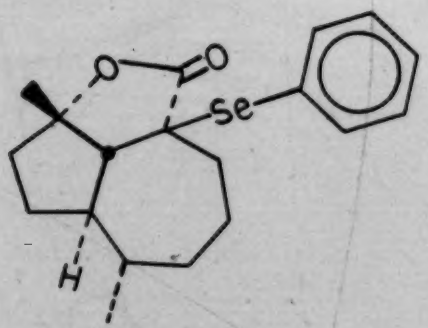
214



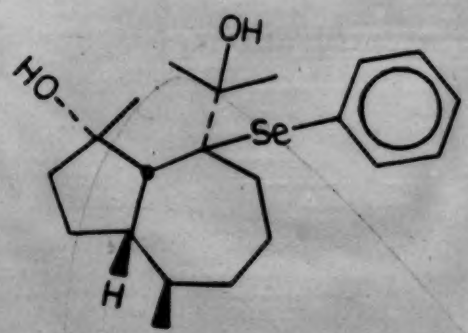
215



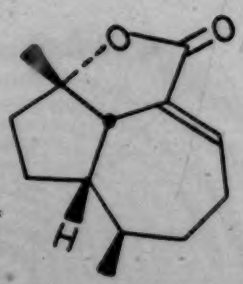
216



217

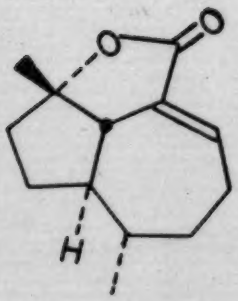


218

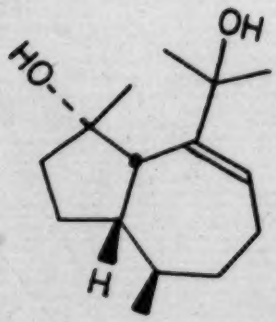


219

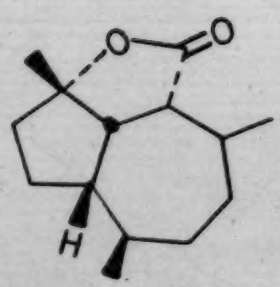
absorption at 1740 cm^{-1} and the carbon-carbon double bond absorption at 1670 cm^{-1}. The pmr spectrum displayed resonance signals at δ 0.91 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.36 (s, 3H) for the C-1 methyl protons, δ 2.24-2.60 (m, 3H) for the allylic protons of C-7 and C-12, and at δ 6.74 (d of t 1H, J = 14 Hz, J' = 2 Hz) for the C-8 vinylic proton coupled to the allylic protons at C-7 (J = 14 Hz) and the allylic proton at C-12 (J = 2 Hz). The mass spectrum also gave a molecular ion peak of 60.23% intensity at 206.1313 for $C_{13}H_{18}O_2$ in agreement with the proposed molecular formula. The infrared spectrum of the dias stereomeric unsaturated lactone 220 also showed an α,β-unsaturated γ-lactone carbonyl absorption at 1740 cm^{-1} and a (C = C) double bond absorption at 1670 cm^{-1}. Its pmr spectrum displayed signals at δ 6.67 (m, 1H) for the vinylic proton, δ 3.17 (br. m, 1H) for the C-12 allylic methine proton, δ 2.3-2.6 (m, 2H) for the C-7 allylic protons, δ 1.46 (s, 3H) for the C-1 methyl protons and at δ 1.1 (d, 3H, J = 5 Hz) for the C-5 methyl protons. The mass spectrum also gave a molecular ion peak of 78.56% intensity at 206.1307 for $C_{13}H_{18}O_2$ in agreement with the assigned molecular formula. At this point it was reasoned that as a result of the strain imposed on the molecule by the bridgehead double bond, the lactone carbonyl of 219 and 220 would react with methyllithium or methylmagnesium bromide to a afford 221, the tertiary allylic hydroxyl group of which could be rearranged to the C-7 position with concomittant



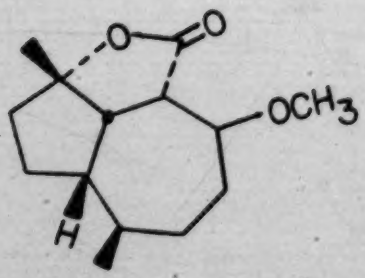
220



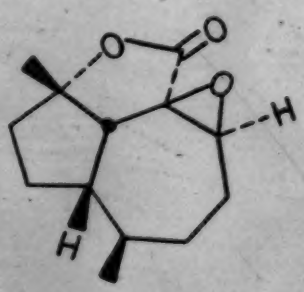
221



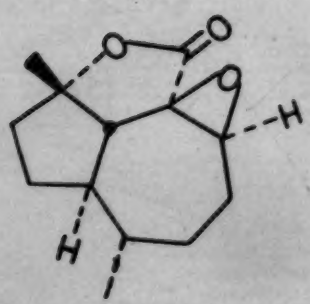
222



223



224



225

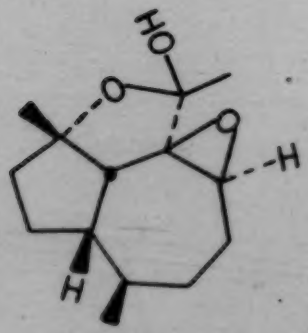
oxidation to introduce the isopropylidene and ketone groups of zierone. It was therefore very much disappointing to find that the expected diol 221 was once again elusive. The reaction of the unsaturated lactone 219 with methyllithium afforded the 1,4-Michael adduct 222. However this unexpected result suggested that perhaps an oxygen functional group could be introduced into the C-8 position of 219 and converted into a ketone which could be protected while the two carbon units of the isopropylidene group was introduced. The unsaturated lactone 219 was therefore treated with sodium methoxide in methanol, but it afforded the methoxy-lactone 223 in only 38% yield with recovery of 219 in 62% yield. Although 223 was identified as such, its low yield made it unattractive as an intermediate compound for our purpose. Its infrared spectrum showed a saturated γ-lactone carbonyl absorption at 1750 cm^{-1} and its pmr spectrum displayed resonance signals at δ 0.90 (3H) for the C-5 methyl protons, δ 1.4 (s, 3H) for the C-1 methyl protons, δ 2.81 (t, 1H, J = 6 Hz) for the C-9 methine proton, δ 3.3 (m, 1H) for the C-8 proton and δ 3.34 (s, 3H) for the methoxy methyl protons, while its mass spectrum gave a molecular weight of 238.1571 for $C_{14}H_{22}O_3$.

The unsaturated lactone 219 was therefore treated with hydrogen peroxide and sodium hydroxide in methanol-tetrahydrofuran mixture to give the α,β-epoxy-lactone 224 in 95% yield. The epoxide 224 was also affordable from 219, albeit in 65% yield by treatment of 219 with m-chloroperbenzoic

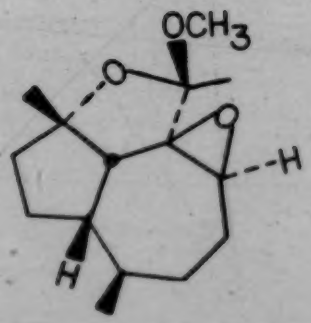
acid. The diastereomeric epoxy-lactone 225 was also prepared in 60% yield by treatment of the unsaturated lactone 220 with m-chloroperbenzoic acid. The expected epoxidation of the carbon-carbon double bond from the sterically less hindered β-face of the molecule explains the assigned stereochemistry of the epoxides. The infrared spectrum of the epoxy-lactone 224 showed a γ-lactone carbonyl absorption at 1775 cm^{-1} due to the presence of the α,β-epoxy moiety. Its pmr spectrum displayed resonance signals at δ 2.44 (t, 1H, J = 1 Hz) for the C-8 proton, δ 2.11 (d, 1H, J = 6 Hz) for the C-12 methine proton, δ 1.54 (s, 3H) for the C-1 methyl protons and δ 0.94 (d, 3H, J = 5 Hz) for the C-5 methyl protons. The mass spectrum also gave a molecular ion peak at 222.1258 for $C_{13}H_{18}O_3$, in agreement with the expected molecular formula. The epoxy-lactone 224 was treated with methyllithium in ether at -78°C to afford an epimeric mixture of hemiketals 226 in 98% yield. The infrared spectrum of 226 showed a hydroxyl group absorption at 3600 cm^{-1} and 3520 cm^{-1}. The pmr spectrum indicated the presence of isomeric hemiketals with signals at δ 1.46, 1.32 (both s, 3H total) for the C-1 methyl protons, δ 2.96, 3.13 (both t, 1H total, J = 5 Hz each) for the C-8 proton and δ 0.94 (d, 3H, J = 5 Hz) for the C-5 methyl protons. Although the mass spectrum did not give a molecular ion peak for the molecule, $C_{14}H_{22}O_3$, it did give a molecular ion of 100% intensity at 220.1466 for $C_{14}H_{20}O_2$ corresponding to the dehydrated species. Upon standing at room temperature the hemiketals

decomposed slowly. It was therefore treated with boron trifluoride etherate shortly after its preparation to afford the unsaturated ketone 229 in 40% yield. However when the epimeric hemiketal mixture was treated with sodium hydride followed by methylation with methyl iodide in tetrahydrofuran it afforded a single methylated derivative 227 in 100% yield, presumably arising from equilibration of the hemiketal with accompanying kinetic methylation of the alkoxide from the sterically less hindered β-face of the molecule to give the ketal 227. When 227 was treated with boron trifluoride etherate in diethyl ether it afforded the unsaturated ketone 229 in 75% yield. Although the infrared spectrum of the epoxy-ketal 227 was not of much diagnostic value its pmr spectrum displayed resonance signals at δ 3.36 (d, 1H, J = 6 Hz) for the C-12 methine proton which is deshielded by both the oxirane and methoxy oxygen atoms, δ 3.14 (s, 3H) for the methoxy methyl protons, δ 2.92 (t, 1H, J = 3 Hz) for the C-8 proton, δ 1.47 (s, 3H) for the methyl protons at the ketal linkage, δ 1.18 (s, 3H) for the C-1 methyl protons and δ 0.92 (d, 3H, J = 5 Hz) for the C-5 methyl protons. The pmr spectrum clearly proved the assigned structure. The mass spectrum gave a molecular ion peak of low intensity at 252.1732 for the parent molecule as well as a base peak at 220.1466 for $C_{14}H_{20}O_2$ corresponding to loss of methanol. The epoxy lactone 225 was also treated with methyllithium and the hemiketal was methylated with methyl iodide to give a single epoxy-ketal 228 in 82% yield from 225. The proton

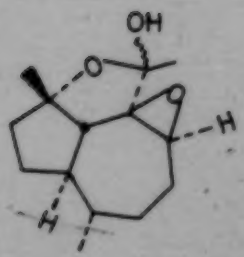
magnetic resonance spectrum of 228 portrayed signals at δ 0.91 (d, 3H, J = 5 Hz) for the C-5 methyl protons, δ 1.25 (s, 3H) for the C-1 methyl protons, δ 2.88 (t, 1H, J = 5 Hz) for the C-8 proton forming part of the oxirane ring, δ 3.16 (s, 3H) for the methoxy methyl protons, δ 1.47 (s, 3H) for the remaining methyl protons. Its mass spectrum expectedly displayed similar characteristics as that of 227. The infrared spectrum of the unsaturated ketone 229 showed the ketone absorption at 1660 cm^{-1} and a much more intense carbon-carbon double bond absorption at 1580 cm^{-1}. Its proton magnetic resonance spectrum portrayed resonance signals at δ 1.32 (s, 3H) for the C-1 methyl protons, δ 2.12 (s, 3H) for the vinylic C-10 methyl protons and δ 0.95 (d, 3H, J = 5 Hz) for the C-5 methyl protons. Its mass spectrum gave a parent molecular ion peak as its base peak at 220.1466 corresponding to $C_{14}H_{20}O_2$ in agreement with the assigned molecular formula. Attempts to introduce the remaining carbon unit of zierone into 229 via a 1,4-Michael type addition of a methylide with methyllithium-cuprous iodide or with methylmagnesium bromide-cuprous bromide complex to afford the ketone 230 which in principle could be dehydrated to afford zierone were futile. An inseparable complex mixture of non-ketonic products was obtained. As a consequence of these negative results it was reasoned that the cyclopropyl derivative 231 could be reductively cleaved to afford 230. A direct formation of the cyclopropyl derivative 231 by treatment of the



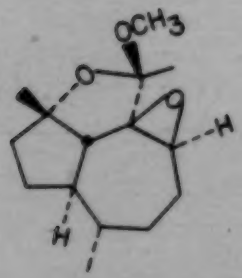
226



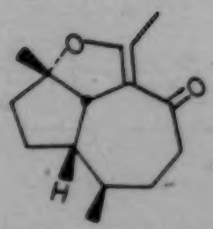
227



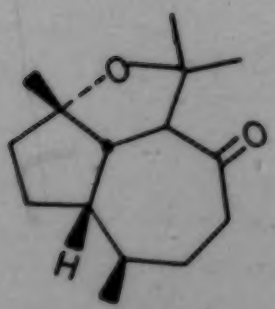
227a



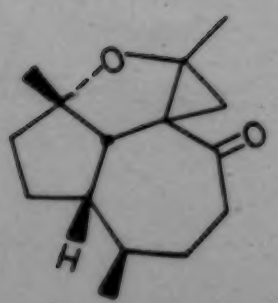
228



229

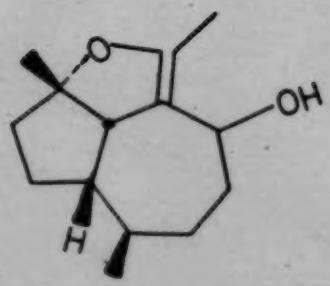


230

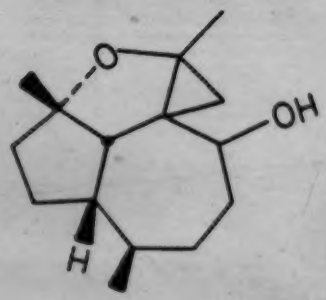


231

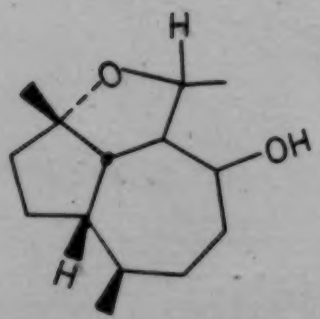
unsaturated ketone 229 with diazomethane and catalylic amount of palladium acetate[70] resulted in complete recovery of the starting material. In order to enhance the olefinic bond for cyclopropanation attempts were made to reduce the ketone functionality to afford the allylic alcohol 232 as it has been shown by Corey et al.[71] that the Simmons-Smith reaction is facilitated by such a hydroxyl substituent. Cyclopropanation of 232 was expected to give the cyclopropyl derivative 233 which could be oxidized to afford the ketone 231. Reduction of the ketone moiety with lithium aluminum hydride or with diisobutylaluminum hydride resulted in the formation of a mixture of product. Separation of the products by column chromatography on silica gel afforded the major product in only 30% yield, however the structure of this product is uncertainly assigned as 234. Although its pmr spectrum suggested the structure of 234, the mass spectrum gave a molecular ion peak corresponding to dimeric compounds of 234. Lastly an attempt made to ketalize 229 by treatment with ethylene glycol and p-toluenesulfonic acid was also futile as it resulted in the formation of a mixture of products. After column chromatographic separation on silica gel, followed by preparative thin layer chromatography the major product was isolated in 29% yield. Although its pmr spectrum portrayed clear signals at δ 0.94 (d, 6H, J = 5 Hz), δ 1.47 (s, 6H), δ 1.7 (s, 6H), δ 6.3 (d, 2H, J = 8 Hz), and δ 4.7 (s, 1H), and its infrared spectrum showed absorption bands at 1700 cm^{-1} and 1610 cm^{-1}, no



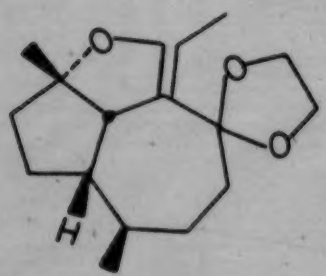
232



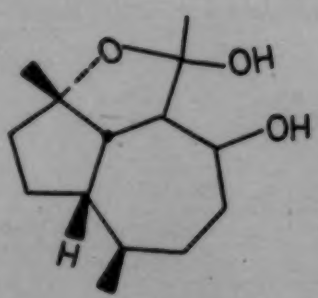
233



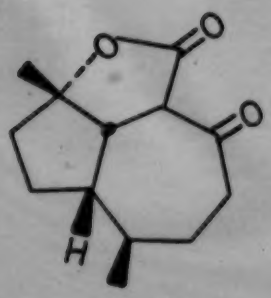
234



235



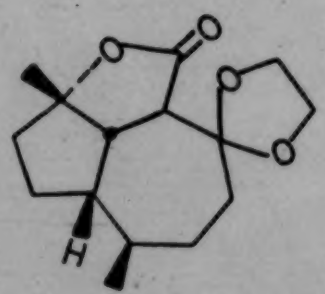
236



237

tentative structure could be assigned to this compound as its mass spectrum gave a molecular ion peak at 404.2718 as its base peak corresponding to $C_{28}H_{36}O_2$. At this point it was decided to temporarily discontinue the investigations along the proposed scheme VIII due to exhaustion of the unsaturated ketone.

As a result of the observations made in pursuit of the scheme VIII, I would like to conclude that further investigations needed to complete the total synthesis of zierone could explore the possibility of the use of the unsaturated lactone 220. This lactone could be converted into the keto-lactone 237 via hydroboration followed by oxidation of the hydroxy-hemiketal 236. Protection of the ketone functionality of 236, followed by Grignard reaction of the ketal-lactone 238 with methyllithium or with methylmagnesium bromide could then afford the desired intermediate 235. This could then be cyclopropanated as previously outlined.



238

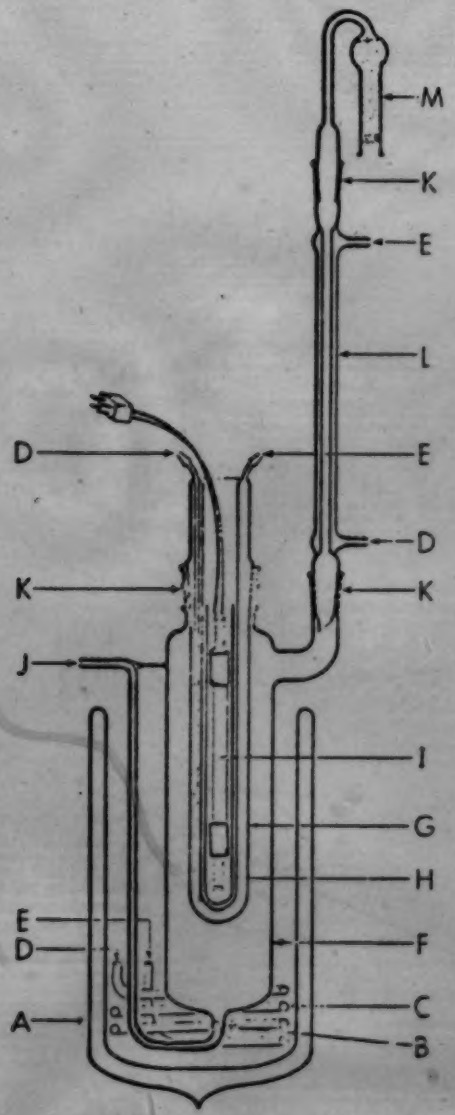


Fig. 1. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

CHAPTER V: EXPERIMENTAL

General

Elemental analysis were performed by the microanalytical laboratory of this department. Calculations were done using the following atomic weights. C 12, H 1, O 16, S 32, Se 80. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin Elmer Model 337 or 457 infrared spectrophotometer. Nuclear magnetic resonance (pmr) spectra were recorded on Varian A-60, HA-100 and HA 100/Digilab spectrometers; using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra were recorded using A.E.I. Model MS-2 or MS-9 mass spectrometers. Mass spectrum is abbreviated ms.

Materials

Silica gel 60, 0.040-0.63 mm particle size, 230-400 mesh ASTM was used as adsorbent for flash chromatography, and silica gel 60-120 mesh was used as adsorbent for column chromatography. 1,2-Dimethoxyethane (DME), diethyl ether (ether), tetrahydrofuran (THF) and benzene used for reactions were freshly distilled from lithium aluminum hydride. Pyridine was heated at reflux temperature over potassium hydroxide and then distilled. 2-Cyclopentenone (74) was prepared from a mixture of 3,4- and 3,5-cyclopentenediol (Research Organic/Inorganic Chemical Corp.)

according to the known procedure.[72] 2-Carbomethoxycyclopentanone was prepared by Dieckmann condensation of dimethyl adipate according to the reported procedure.[73]

1-Acetoxy-2-carbomethoxycyclopentene (75).

To a mechanically stirred solution of 2-carbomethoxycyclopentanone (340.10 g, 2.39 mol) in pyridine (378.36 g, 4.79 mol, 386.08 ml) maintained at 0°C under a nitrogen atmosphere was added acetyl chloride (296.61 g, 3.78 mol, 296.6 ml) over a period of 1.5 hr. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 36 hr. After cooling to 0°C, ether (600 ml) was added and the resulting mixture filtered. The filtrate was acidified with 10% aqueous sulfuric acid and the ethereal layer separated and washed with saturated aqueous sodium chloride solution. The aqueous layer was extracted with 3 x 300 ml of chloroform and the chloroform layers washed with brine. The combined organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent removed by distillation. The product was finally distilled under vacuum at 74-76°C/0.5 torr to afford 352.55 g (80% yield) of 1-acetoxy-2-carbomethoxycyclopentene (75). ir (neat) 1780 (enol acetate), 1725 ($-COOCH_3$) and 1665 cm^{-1} (C=C); pmr ($CDCl_3$) δ 3.63 (s, 3H, $-COOCH_3$) and 2.3 (s, 3H, CH_3-COO-).

7-Acetoxy-1-carbomethoxytricyclo[5.3.0.$0^{2,6}$]decan-3-one (101, 102) and 1-acetoxy-7-carbomethoxytricyclo[5.3.0.$0^{2,6}$]-decan-3-one (103, 104).

A solution of 331.79 (1.80 mol) of 1-acetoxy-2-carbomethoxycyclopentene (75) in 600 ml of benzene was placed in the photochemical reaction vessel (Fig. 1) and 8.40 g (0.11 mol) of 2-cyclopentene-1-one was added. Dry nitrogen gas was bubbled through the reaction chamber to agitate the solution. Crushed ice and water were poured into the outer dewar flask containing the reaction vessel to cool the reaction mixture. The reaction mixture was irradiated with a 450W Hanovia high pressure quartz mercury-vapour lamp using a pyrex filter for 24 hr. After this period, 7.04 g (0.087 mol) of 2-cyclopentene-1-one was added to the reaction mixture and irradiated for another 24 hr. The process of adding 2-cyclopentene-1-one was repeated five times irradiating for 24 hr after each addition of 6.87 g (0.085 mol), 5.91 g (0.075 mol), 5.77 g (0.07 mol), 5.34 g (0.065 mol) and 5.056 g (0.06 mol). The solvent was distilled at normal atmospheric pressure and the excess olefin 75 was distilled under vacuum at 75°C/0.5 torr leaving an oily residue containing the photocycloadducts 101→104. This crude product was thioketalized (see below) without further purification.

In a similar experiment, 6.0 g (0.073 mol) of

2-cyclopentene-1-one and 201.95 g (1.098 mol) of 1-acetoxy-2-carbomethoxycyclopentene (75) were irradiated for 24 hr in 300 ml of methanol. After the usual distillation the crude oily product was purified by column chromatography on silica gel eluting with 20% diethyl ether in n-hexane followed by further purification by high pressure liquid chromatography using 20% petroleum ether (30-60°C) in diethyl ether as eluent to afford 4.93 g (0.0185 mol; 25% yield) of 101.

In a third similar experiment, 6.0 g (0.073 mol) of 2-cyclopentene-1-one and 201.95 g (1.098 mol) of 1-acetoxy-2-carbomethoxycyclopentene were irradiated in 300 ml of isopropanol for 24 hr. After recovery of the excess olefin 75 the residual oily product was purified by column chromatography (thrice) on silica gel using 20% diethyl ether in n-hexane to afford an oily product 101 (9.86 g, 0.037 mol; 50% yield): ir ($CHCl_3$) 1750 (ketone), 1725 and 1735 cm^{-1} (esters); pmr ($CDCl_3$) δ 2.02 (s, 3H, -OOC-$\underline{CH_3}$), 3.65 (s, 3H, -COO$\underline{CH_3}$), 2.10 (d, 1H, J = 7 Hz, C-2 proton) and 1.6-2.9 (m, 11H); ms M^+ 266.117 (calcd. for $C_{14}H_{18}O_5$: 266.1155). Anal. Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.77, O 30.7. Found: C 63.15, H 6.87, O 30.36.

In the third experiment using isopropanol as solvent followed by column chromatography as described above another oily product 103 (1.95 g, 0.007 mol; 10% yield) was obtained. ir ($CHCl_3$) 1750 (ketone) and 1720 cm^{-1} (esters); pmr ($CDCl_3$) δ 1.98 (s, 3H, $\underline{CH_3}$-COO-), 3.66 (s, 3H, $\underline{CH_3}$OOC-) and 1.6-2.9 (m, 12H); ms M^+ 266.1117 (calcd. for $C_{14}H_{18}O_5$: 266.1155).

Anal. Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.77, O 30.07. Found: C 62.93, H 6.75, O 29.99.

7-Acetoxy-1-carbomethoxy-3,3-ethylenedithiotricyclo-[5.3.0.$0^{2,6}$]decane (96 and 98) and 1-acetoxy-7-carbomethoxy-3,3-ethylenedithiotricyclo[5.3.0.$0^{2,6}$]decane (95 and 97).

Crude photocycloaddition products (50.0 g) obtained from above with benzene as solvent were dissolved in 180.0 ml of 1,2-ethanedithiol. The solution was cooled in an ice-water bath and stirred with the slow addition of 18.7 ml of boron trifluoride etherate solution. The reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 6 hr, poured into 600 ml of ice-cold 4N aqueous sodium hydroxide solution and extracted with 3 x 400 ml of chloroform. The chloroform layers were washed with 4N aqueous sodium hydroxide solution (2 x 150 ml) and then with saturated sodium chloride solution (2 x 300 ml). The chloroform solution was dried with anhydrous magnesium sulfate and concentrated to give a residual oily product. The remaining photocycloaddition product mixture was similarly treated. The combined product was purified by silica gel column chromatography eluting with 15% ether in n-hexane to afford two different oily fractions and a mixture of these two fractions in a total of 199.49 g (0.58 mol; 60% yield based on the initial photocycloaddition

reaction). Further chromatographic purification of the fraction with higher R_f (per tlc analysis) followed by crystallization from n-pentane-ether solution afforded a crystalline product 95 (49.80 g, 0.146 mol; 15% yield): m.p. 85.5-87.5°C; ir ($CHCl_3$) 1725 and 1735 cm^{-1} (esters); pmr ($CDCl_3$) δ 2.1 (s, 3H, CH_3-COO-), 3.62 (s, 3H, -OOC-CH_3), 3.2 (m, 4H, -S-CH_2-CH_2-S) and 1.5-2.9 (m, 12H). ms M^+ 342.0952 (calcd. for $C_{16}H_{22}O_4S_2$: 342.0956). Anal. Calcd. for $C_{16}H_{22}O_4S_2$: C 56.14, H 6.43, O 18.71, S 18.71. Found: C 56.18, H 6.47, O 18.73, S 18.37.

The mother liquor of 95 was subjected to column chromatography on silica gel eluting with 12% ether in n-pentane to give the thioketal 96 (9.96 g; 3% yield): ir ($CHCl_3$) 1725 and 1735 cm^{-1} (esters); pmr ($CDCl_3$) δ 2.04 (s, 3H, CH_3-COO-), 3.64 (s, 3H, -COO-CH_3), 3.25 (m, 4H, -S-CH_2-CH_2-S-) and 1.6-2.8 (m, 12H) ms M^+ 342.0952 (calcd. for $C_{16}H_{22}O_4S_2$: 342.0956). Anal. Calcd. for $C_{16}H_{22}O_4S_2$: C 56.14, H 6.43, O 18.71, S 18.71. Found: C 55.87, H 6.48, O 18.92, S 18.64.

Similar column chromatography of the slower moving fraction followed by crystallization from n-hexane-ether solution afforded 97 (39.84 g, 0.116 mol; 12% yield): m.p. > 175°C (decomposes); ir ($CHCl_3$) 1735 and 1745 cm^{-1} (esters); pmr ($CDCl_3$) δ 1.98 (s, 3H, CH_3-COO-), 370 (s, 3H, -COOCH_3). 3.35 (m, 4H, -S-CH_2-CH_2-S-), and 1.5-3.0 (m, 12H); ms M^+ 342.0952 (calcd. for $C_{16}H_{22}O_4S_2$: 342.0956). Anal. Calcd. for $C_{16}H_{22}O_4S_2$: C 56.14, H 6.43, O 18.71,

S 18.71. Found: C 56.18, H 6.47, O 18.71, S 18.71.

The mother liquor of 97 was subjected to column chromatography on silica gel eluting with 15% ether in n pentane to give the thioketal 98 (4.98 g, 0.015 mol; 1.5% yield): ir ($CHCl_3$) 1735 and 1745 cm^{-1} (esters); pmr ($CDCl_3$) δ 1.98 (s, 3H, $\underline{CH_3}$-COO-), 3.70 (s, 3H, -COO$\underline{CH_3}$) and 3.35 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-); ms M^+ 342.0952 (calcd. for $C_{16}H_{22}O_4S_2$: 342.0956). Anal. Calcd. for $C_{16}H_{22}O_4S_2$: C 56.14, H 6.47, O 18.71, S 18.71. Found: C 56.26, H 6.52, O 19.11, S 18.64.

1-Acetoxy-7-carbomethoxytricyclo[5.3.0.$0^{2,6}$]decan-3-one (103 and 104) and 7-acetoxy-1-carbomethoxytricyclo-[5.3.0.$0^{2,6}$]decan-3-one (101 and 102).

To a solution of crystalline 95 (7.0 g, 20.47 mmol) in 56 ml of acetonitrile at room temperature, a solution of mercuric chloride (27.75 g, 0.102 mol) in 168 ml of acetonitrile-water (2:1) mixture was added with stirring. The reaction mixture was stirred for 6 hr at room temperature. The solid residue was filtered off and washed with chloroform. The filtrate was extracted with chloroform (3 x 150 ml) and the organic layers washed with saturated aqueous ammonium acetate (2 x 150 ml) and then with brine. The combined organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash

evaporation to afford an oily product which was purified by column chromatography on silica gel eluting with 25% ether in n-hexane to give an oily product 103 (5.43 g, 0.0204 mol; 99% yield): ir ($CHCl_3$) 1750 (ketone) 1720 and 1730 cm^{-1} (esters); pmr ($CDCl_3$) δ 1.98 (s, 3H, CH_3-COO-), 3.66 (s, 3H, -COO-CH_3) and 1.6-2.9 (m, 12H); ms M^+ 266.1117 (calcd. for $C_{14}H_{18}O_5$: 266.1155). Anal. Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.77, O 30.07. Found: C 62.93, H 6.73, O 29.99.

The crystalline isomeric thioketal 97 was similarly treated to give a 95% yield of the keto-ester 104. Crystallization from n-pentane-ether solution afforded a crystalline material: m.p. 96.5-97°C; ir ($CHCl_3$) 1750 (ketone C=O) 1725 and 1735 cm^{-1} (esters); pmr ($CDCl_3$)) δ 2.1 (s, 3H, CH_3-COO-), 3.71 (s, 3H, -COOCH_3) and 1.5-3.0 (m, 12H). ms M^+ 266.1151 (calcd. for $C_{14}H_{18}O_5$: 266.1155). Anal. Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.77, O 30.07. Found: C 62.99, H 6.72, O 31.25.

Also, hydrolysis of 96 afforded the keto-ester 101 in 95% yield. The spectral data of 101 has already been given (vide supra).

Similarly hydrolysis of 98 afforded a 90% yield of 102: ir ($CHCl_3$) 1750 (ketone), 1725 and 1735 cm^{-1} (esters); pmr ($CDCl_3$) δ 2.1 (s, 3H, CH_3-COO-), 3.71 (s, 3H, -COO-CH_3) and 1.5-2.9 (m, 12H); ms M^+ 266.1117 (calcd. for $C_{14}H_{18}O_5$: 266.1155).

3,3-Ethylenedithio-1-hydroxy-7-hydroxymethyltricyclo-[5.3.0.$0^{2,6}$]decane (105).

A suspension of lithium aluminum hydride (0.406 g, 10.74 mmol) in 26 ml of ether was stirred at 0°C under a nitrogen atmosphere and a solution of the diester 95 (1.068 g, 3.121 mmol) in 10 ml of ether was added. The reaction mixture was stirred at 0°C for 1.5 hr and then diluted with 10 ml of wet ether followed by dropwise addition of saturated aqueous sodium chloride solution until the solid turned grey. Anhydrous sodium sulfate was added to the reaction mixture and stirred for 30 minutes. The solid residue was filtered off and washed with ether. The filtrate was concentrated and the crude product purified by column chromatography on silica gel eluting with 30% ether in n-hexane to afford 105 (806.73 mg; 95% yield). Crystallization from n-hexane-ether solution afforded a crystalline compound: m.p. 89.5°C; ir ($CHCl_3$) 3420 and 3510 cm^{-1} (-OH); pmr ($CDCl_3$) δ 3.29 (s, 2H, -O-$\underline{CH_2}$-) and 3.25 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-); ms M^+ 272.0909 (calcd. for $C_{13}H_{20}O_2S_2$: 272.0904). Anal. Calcd. for $C_{13}H_{20}O_2S_2$: C 57.35, H 7.36, O 11.79, S 23.53. Found: C 57.35, H 7.36, O 11.84, S 23.60.

3,3-Ethylenedithio-7-hydroxymethyltricyclo[5.3.0.$0^{2,6}$]decane (114) and 5-hydroxy-11-oxatetracyclo[7.2.1.0.$^{5,9}0^{4,12}$]-dodecane (115) from 96.

Lithium aluminum hydride reduction of 96 (1.068 g, 3.121 mmol) following the procedure used for the reduction of 95 afforded two products 114 (212.30 mg; 25% yield) and 115 (421.60 mg; 75% yield) after column chromatography of the crude product on silica gel eluting with 30% ether in n-hexane. The following spectral data were obtained for these products.

114: ir ($CHCl_3$) 3500 cm^{-1} (OH); pmr ($CDCl_3$) δ 3.9 (d, 2H, J < 1 Hz, HO-CH_2-), 3.25 (m, 4H, -S-CH_2-CH_2-S-) and 1.2-2.5 (m, 12H); ms M^+ 272.0909 (calcd. for $C_{13}H_{20}O_2S_2$: 272.0904). Anal. Calcd. for $C_{13}H_{20}O_2S_2$: C 57.35, H 7.36, O 11.72, S 23.42. Found: C 57.47, H 7.42, O 11.81, S 23.38.

115: ir ($CHCl_3$) 3400 cm^{-1} (OH); pmr ($CDCl_3$) δ 4.2-4.5 (m, 2H, -O<u>H</u> and C-1 proton), 3.5, 4.2 (both d, 1H each, J = 12 Hz, -O-CH_2-) and 1.2-3.5 (m, 12H); ms M^+ 180.1148 (calcd. for $C_{11}H_{16}O_2$: 180.1152).

5-Hydroxy-11,14-dithiotetracyclo[7.5.1.0.$^{5,9}0^{4,15}$]pentadec-1-ene (116).

To a solution of 114 (166.95 mg, 0.614 mmol) in 3 ml of

dry pyridine was added 174.9 mg (0.916 mmol) of p-toluenesulfonyl chloride. The reaction mixture was stirred at room temperature for 24 hr. The mixture was then poured into 50 ml of 2N aqueous hydrochloric acid and extracted with chloroform (2 x 20 ml). The chloroform layers were washed with 50 ml of the acid and then with water, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. The residual oily product was purified by column chromatography on silica gel, eluting with 10% ether in n-hexane to afford 116 (94.15 mg; 60% yield): ir ($CHCl_3$) 3500 (-OH) and 1690 cm^{-1} (C=C); pmr ($CDCl_3$) δ 5.9 (t, 1H, J < 1 Hz, -CH=C-S-), 3.28 (t, 2H, J = 3 Hz, =C-S-CH_2-) and 2.6-3.0 (m, 4H, -CH_2-S-CH_2-); ms M^+ 254.1164 (calcd. for $C_{13}H_{18}OS_2$: 254.1162).

10-Ethylenedithio-6-methylenebicyclo[5.3.0]decan-2-one (106)

To a solution of the diol 105 (1.80 g, 6.62 mmol) in 20 ml of dry pyridine was added p-toluenesulfonyl chloride (2.0 g, 10.53 mmol) with stirring. The reaction mixture was stirred at room temperature for 48 hr and then poured into 20 ml of ice-cold 2N aqueous sodium hydroxide solution and extracted with chloroform (2 x 40 ml). The chloroform solution was dried with anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by column chromatography eluting with 15% ether in n-hexane afforded 109 (1.68 g; 99.92% yield). Crystallization from n-hexane

afforded crystalline 109: m.p. 64-65°C; ir ($CHCl_3$) 1705 (ketone), 905, 1160, 1315 and 1680 cm^{-1} ($C=CH_2$); pmr ($CDCl_3$) δ 4.8, 4.86 (two singlets, 1H, each, $=CH_2$), 3.16 (d, 1H, J = 9 Hz, -CH-CO-), 3.25 (m, 4H, $-S-CH_2-CH_2-S-$), 2.26 (t, 3H, J = 5 Hz, allylic protons) and 1.4-2.8 (m, 8H); ms M^+ 254.1164 (calcd. for $C_{13}H_{18}OS_2$: 254.1131). Anal. Calcd. for $C_{13}H_{18}OS_2$: C 60.94, H 7.81, O 6.25, S 25.0, Found: C 61.59, H 7.06, O 6.49, S 25.42.

Hydrolysis of 105

To a solution of 105 (595.16 mg, 2.188 mmol) in 6 ml of acetonitrile was added a solution of mercuric chloride (2.498 g, 9.2 mmol) in 18 ml of acetonitrile-water (2:1) mixture. The reaction mixture was stirred at room temperature for 4 hr. The reaction mixture was then filtered to remove the inorganic solids and the filtrate was diluted with 20 ml of water and extracted with chloroform (2 x 50 ml). The chloroform extracts were washed with saturated aqueous ammonium acetate (2 x 50 ml) and brine. The combined organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residual products was purified by column chromatography on silica gel eluting with 35% ether in n-hexane to afford three products, 109 (115.75 mg; 26.99% yield), 110 (114.56 mg; 26.99% yield) and 111 (177.24 mg; 29.78% yield).

2-(3'-oxocyclopentyl)-2-hydroxymethylcyclopentanone (109), ir ($CHCl_3$) 3450 (OH) and 1740 cm^{-1} (ketone);

pmr ($CDCl_3$) δ 5.85 (br. s, -OH), 3.60 (s, 2H, -O-CH_2-) and 1.2-2.9 (m, 13H); ms M^+ 196.1098 (calcd. for $C_{11}H_{16}O_3$: 196.1084).

3-(1'-hydroxymethyl-2'-oxocyclopentyl)-1-mercapto ethylenethiocyclopentene (110): This compound was identified as its diester (vide infra).

Spiro[2-oxabicyclo[3.3.0]decane-4-1'-cyclopentane] (111) ir ($CHCl_3$) 1750 and 1745 cm^{-1} (ketone); pmr ($CDCl_3$) δ 4.38 (d, 1H, J = 6 Hz, O=C-CH-O-), 3.65, 3.69 (both d, 1H each, J = 7 Hz each, -O-CH_2-), 3.05 (dd, 1H, J = 7 Hz, J' = 6 Hz, -CH-) and 1.5-2.7 (m, 10H); ms M^+ 194.1969 (calcd. for $C_{11}H_{14}O_3$: 194.1955).

2-Acetoxymethyl-2-(3'-oxocyclopentyl)cyclopentanone (112).

To a solution of the hydroxy-diketone 109 (100.0 mg, 0.51 mmol) in pyridine (2 ml) was added acetic anhydride (1 ml). After stirring at room temperature for 20 hr the reaction mixture was poured into 20 ml of 2N aqueous hydrochloric acid and extracted with chloroform (2 x 20 ml). The organic layers were washed with 20 ml of the acid and water. The combined chloroform solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residue on silica gel eluting with 10% ether in benzene afforded 112 (97.14 mg; 80% yield): ir ($CHCl_3$) 1735 (ester) and 1750 cm^{-1} (ketone); pmr ($CDCl_3$) δ 4.15 (s, 2H, -O-CH_2-), 2.1 (s, 3H, CH_3-COO-)

and 1.5-2.7 (m, 13H); ms m/e (M-15) 223.0986 (calcd. for $C_{12}H_{15}O_4$: 223.0988) and (M-42) 196.1098 (calcd. for $C_{11}H_{15}O_3$: 196.1086).

3-(1'-Acetoxymethyl-2'-oxocyclopentyl)-1-thiolacetylethylene-thiocyclopentene (113).

To a solution of 110 (115.0 mg, 0.423 mmol) in dry pyridine (2 ml) was added acetic anhydride (1 ml). The resulting solution was stirred at room temperature for 20 hr and then poured into 20 ml of 2N aqueous hydrochloric acid and extracted with chloroform (2 x 20 ml). The organic layers were washed with 20 ml of the acid and water. The combined chloroform solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residue on silica gel eluting with 10% ether in benzene afforded 113 (90.31 mg; 60% yield): ir ($CHCl_3$) 1735 (CH_3-COO-), 1700 (CH_3-CO-S-) and 1650 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.05 (s, 3H, CH_3-COO-), 2.35 (s, 3H, CH_3-CO-S-), 4.15 (d, 2H, J = 2 Hz, -O-CH_2-), 5.50 (m, 1H, =CH), 3.0-3.2 (m, 4H, -S-CH_2-CH_2-S-) and 1.2-2.6 (m, 11H); ms m/e (M-60) 296.0921 (calcd. for $C_{15}H_{20}O_2S_2$: 296.0927).

3,3-Ethylenedithio-1-hydroxy-7-hydroxymethyltricylo-[5.3.0.$0^{2,6}$]decane (117).

A suspension of lithium aluminum hydride (0.406 g, 10.7 mmol) in 26 ml of ether was stirred at 0°C under a nitrogen atmosphere. A solution of the diester 97 (1.059 g, 3.10 mmol) in 10 ml of ether was added. The reaction mixture was stirred at 0°C for 1.5 hr and then diluted with wet ether. Saturated aqueous sodium chloride solution was slowly added until the solid turned grey. Anhydrous sodium sulfate was added and the mixture was stirred for 30 min. The solid residue was filtered off and washed with ether. The filtrate was concentrated and the crude product purified. by column chromatography on silica gel eluting with 30% ether in n-hexane to afford 117 (826.34 mg; 98% yield): ir ($CHCl_3$) 3400 cm^{-1} (OH); pmr ($CDCl_3$) δ 3.7 (s, 2H, -O-CH_2-), 3.2-3.4 (m, 4H, -S-CH_2-CH_2-S-) and 0.9-3.1 (m, 14H); ms M^+ 272.0909 (calcd. for $C_{13}H_{20}O_2S_2$: 272.0904). Anal. Calcd. for $C_{13}H_{20}O_2S_2$: C 57.35, H 7.36, O 11.79, S 23.53. Found: C 57.29, H 7.46, O 11.78, S 23.35.

10-Ethylenedithio-6-methylenebicyclo[5.3.0]decan-2-one (118) from (117).

To a solution of the diol 117 (1.05 g, 3.86 mmol) in dry pyridine (20 ml) was added p-toluenesulfonyl chloride

(1.167 g, 6.14 mmol) with stirring. The reaction mixture was stirred at room temperature for 48 hr and then poured into 20 ml of ice-cold 2N sodium hydroxide solution and extracted with chloroform (2 x 40 ml). The chloroform layers were washed with 1N aqueous hydrochloric acid and brine solutions. The combined chloroform solution was dried with anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by column chromatography on silica gel eluting with 15% ether in n-hexane afforded 118 (1.03 g; 95% yield). Crystallization from n-hexane at -15°C afforded crystalline 118: m.p. 64-65°C; ir ($CHCl_3$) 1705 (ketone), 905, 1160, 1315 and 1680 cm^{-1} ($C=CH_2$); pmr ($CDCl_3$) δ 4.8, 4.86 (two singlets, 1H each, $=CH_2$), 3.16 (d, 1H, J = 9 Hz, $-\overset{1}{C}H-CO-$), 3.25 (m, 4H, $-S-CH_2-CH_2-S-$), 2.26 (t, 3H, J = 5 Hz, allylic protons) and 1.4-2.8 (m, 8H); ms M^+ 254.1164 (calcd. for $C_{13}H_{18}OS_2$: 254.1131). Anal. Calcd. for $C_{13}H_{18}OS_2$: C 60.94, H 7.81, O 6.25, S 25.0. Found C 61.59, H 7.06, O 6.49, S S 25.42.

3,3-Ethylenedithio-7-hydroxy-1-hydroxymethyltricyclo-[5.3.0.$0^{2,6}$]decane (108).

A suspension of lithium aluminum hydride (0.0203 g, 5.4 mmol) in ether (15 ml) was stirred at 0°C under a nitrogen atmosphere and a solution of the diester 98 (0.534 g, 1.56 mmol) in ether (10 ml) was added. The reaction mixture

was stirred at 0°C for 1.5 hr. The usual work up followed by column chromatography of the crude product on silica gel eluting with 30% ether in n-hexane gave the dihydroxy-thioketal 108 (414.95 mg; 97.95% yield): ir ($CHCl_3$) 3400 cm^{-1} (OH); pmr ($CDCl_3$) δ 3.68 (s, 2H, -O-CH_2-) and 3.3 (m, 4H, -S-CH_2-CH_2-S-); ms M^+ 272.0909 (calcd. for $C_{13}H_{20}O_2S_2$: 272.0904). Anal. Calcd. for $C_{13}H_{20}O_2S_2$: C 57.35, H 7.36, O 11.79, S 23.52. Found: C 57.47, H 7.42, O 11.81, S 23.38.

10-Methylthioethylenethio-6-methylenebicyclo[5.3.0]dec-10-ene-2-one (119) from 106 and 118.

Sodium hydride (25.98 mg, 1.08 mmol) was added to a solution of 106 (237.1 mg, 0.933 mmol) in dimethoxyethane (25 ml) under a nitrogen atmosphere. The mixture was stirred for 10 min and methyl iodide (279.51 mg, 2.12 mmol) was added. The resulting reaction mixture was stirred for 18 hr at room temperature. The product was poured slowly into cold water and extracted with ether (2 x 30 ml). The ethereal layers were washed with saturated sodium chloride solution, combined, dried with anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 15% ether in n-hexane afforded 119 (217.25 mg; 86% yield): ir ($CHCl_3$) 1645 (conjugated ketone) 895, 1120 and 1525 cm^{-1} (=CH_2, C=C); pmr ($CDCl_3$) δ 4.85 (s, 2H, =CH_2), 3.7 (t, 1H, J = 8 Hz,

-CH-C=), 2.19 (s, 3H, CH_3-S-), 2.75 (m, 4H, -S-CH_2-CH_2-S-) and 1.6-3.2 (m, 10H). ms M^+ 268.0958 (calcd. for $C_{14}H_{20}OS_2$: 268.0962).

When 118 was treated under similar conditions it also afforded 119 with identical spectra as above.

6-Carbomethoxybicyclo[5.3.0]decane-2,10-dione (120).

To a solution of 103 (100.0 mg, 0.38 mmol) in methanol (5 ml) was added 2N aqueous sodium hydroxide (1 ml). The resulting solution was stirred at room temperature for 4 hr, acidified with 1N aqueous hydrochloric acid and extracted with chloroform. The chloroform layer was washed with water, dried with anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 25% ether in n-hexane afforded 120 (60.4 mg; 72.36% yield): ir ($CHCl_3$) 1735 (ester), 1705 and 1620 cm^{-1} (β-diketone); pmr ($CDCl_3$) δ 3.68 (s, 3H, -$COOCH_3$) and 1.2-2.3 (m, 13H); ms M^+ 224.1046 (calcd. for $C_{12}H_{16}O_4$: 222.1046). The keto-diester 104 afforded 120 in 72% yield under similar conditions.

2-Acetoxy-6-carbomethoxybicyclo[5.3.0]dec-1-en-10-one (121) and 10-acetoxy-6-carbomethoxybicyclo[5.3.0]dec-10-en-2-one (122).

To a solution of 120 (120.0 mg, 0.54 mmol) in dry

pyridine (3 ml) was added acetic anhydride (1 ml). The reaction mixture was stirred at room temperature for 3 hr. Dry benzene (2 ml) was added and the solvent removed by flash evaporation. This process was repeated until there was very little pyridine and acetic anhydride left. The residue was purified by column chromatography on silica gel eluting with 20% ether in n-hexane to afford an isomeric mixture of 121 and 122 [114.0 mg; 80% yield; 121:122 (~9:1) by pmr]: 121: ir ($CHCl_3$) 1720 (cyclopentenone), 1735 (ester(, 1765 (CH_3-COO-, enol acetate) and 1640 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.20 (s, 3H, CH_3-COO-) and 3.68 (s, 3H, -$COOCH_3$). ms M^+ 266.1112 (calcd. for $C_{14}H_{18}O_5$: 266.1116).

1-Acetoxy-7-carbomethoxy-3-hydroxy-3-methyltricyclo-[5.3.0.$0^{2,6}$]decane (123), 1-acetoxy-7-acetyl-3-hydroxy-3-methyltricyclo[5.3.0.$0^{2,6}$]decane (124) and 6-carbomethoxy-10-hydroxy-10-methylbicyclo[5.3.0]decane-6-one (125).

A solution of the keto-diester 104 (1.0 g, 3.76 mmol) in ether (150 ml) was stirred under a nitrogen atmosphere at -78°C and methyllithium (4.14 mmol; 2.07 ml of 2.0M solution in ether) was added slowly with stirring. The reaction mixture was stirred at -78°C for 2 hr and then poured into 100 ml of ice-cold saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer extracted with 150 ml of ether. The ethereal layers were

washed with saturated sodium choloride solution, dried with anhydrous magnesium sulfate, filtered and concentrated to afford an oily residue. Purification of the residue by column chromatography on silica gel eluting with 15% ether in n-pentane afforded 123 (742.11 mg; 70% yield), 124 (110.77 mg; 10% yield) and 125 (90.29 mg; 10% yield). The spectral data of these compounds are as follows.

123: ir ($CHCl_3$) 3500 (OH) and 1725 cm^{-1} (esters); pmr ($CDCl_3$) δ 4.15 (s, 1H, -O-H), 3.75 (s, 3H, $-COOCH_3$), 2.55 (d, 1H, J = 9 Hz, C-2 proton), 1.96 (s, 3H, CH_3COO-), 1.18 (s, 3H, $CH_3-\overset{|}{C}(OH)-$) and 1.5-3.5 (m, 11H); ms m/e (M-42) 240.1353 (calcd. for $C_{13}H_{20}O_4$: 240.1353) and M-60 222.1256 (calcd. for $C_{13}H_{18}O_3$: 222.1251).

124: ir ($CHCl_3$) 3500 (OH), 1710 ($CH_3-\overset{|}{C}=O$) and 1725 cm^{-1} (ester); pmr ($CDCl_3$) δ 2.26 (s, 3H, $CH_3-\overset{|}{C}=O$), 2.02 (s, 3H, CH_3COO-), 1.24 (s, 3H, $CH_3-\overset{|}{C}(OH)-$), 4.15 (br. s, 1H, -O-H) and 1.5-3.2 (m, 12H).

125: ir ($CHCl_3$) 3500 (OH), 1710 (ketone) and 1725 cm^{-1} (ester). Upon treatment with sodium methoxide in methanol it afforded 126 (vide infra).

6-Carbomethoxy-10-methylbicyclo[5.3.0]dec-10-en-2-one (126).

To a solution of 124 (740.0 mg, 2.62 mmol) in methanol (70 ml) was added 2N methanolic sodium methoxide (10.5 ml). The reaction mixture was stirred at room temperature for 4 hr, cooled to 0°C and acidified with 1N aqueous hydrochloric

acid. The resulting solution was extracted with ether (2 x 100 ml). The ethereal layers were washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate, filtered and the solvent removed to afford an oily product. Purification of the residual oily product by column chromatography on silica gel eluting with 15% ether in n-pentane afforded 126 (582.55 mg; ~100% yield). Crystallization from n-hexane at -20°C gave crystalline 126, m.p. 49.5-50.5°C; ir ($CHCl_3$) 1735 (ester), 1675 (α,β-unsaturated cycloheptanone C=O) and 1615 cm^{-1} (C=C, conjugated to ketone); pmr ($CDCl_3$) δ 3.65 (s, 3H, $-COOCH_3$), 2.1 (s, 3H, $CH_3-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$) and 1.5-3.5 (m, 12H); ms M^+ 222.1263 (calcd. for $C_{13}H_{18}O_3$: 222.1268). Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11, O 21.62. Found: C 69.45, H 8.09, O 23.04.

Attempted methylation of the acid 127; 1,2-Dimethyl-12-oxa-11-oxotricyclo[5.3.2.$^{1,7}O^{2,8}$]undecan-3-one (128).

To a solution of 127 (200.0 mg, 0.962 mmol) in acetone (10 ml) was added potassium carbonate 664.33 mg, 4.81 mmol). After stirring at room temperature for 1 hr, methyl iodide (273.20 mg, 1.924 mmol) was added. The reaction mixture was stirred for 48 hr, filtered and the solvent removed by flash evaporation. The residue was extracted with ether (2 x 20 ml) and the extracts were washed with hydrochloric acid (20 ml), water and saturated sodium chloride solution,

dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with 15% ether in n-hexane afforded 126 (64.07 mg; 30% yield). This was followed by elution with 25% ether in n-hexane to give 128 (137.11 mg; 64.2% yield). The former compound showed the following spectral data: ir ($CHCl_3$) 1700 (ketone) and 1740 cm^{-1} (δ -lactone); pmr ($CDCl_3$) δ 2.22 (s, 3H, C-2 methyl) and 1.35 (s, 3H, C-1 methyl); ms M^+ 222.1263 (calcd. for $C_{13}H_{18}O_3$: 222.1268).

Reaction of 103 with methyllithium

To a solution of the keto-diester 103 (2.0 g, 7.52 mmol) in ether (300 ml) at -78°C under a nitrogen atmosphere, methyllithium (8.28 mmol, 4.14 ml of 2.0M solution in ether) was added slowly. The reaction mixture was stirred at -78°C for 2 hr and then poured into 150 ml of ice-cold saturated ammonium chloride solution. The ethereal layer was separated and the aqueous layer was extracted with 150 ml of ether. The ethereal layers were washed with saturated sodium chloride solution, combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residue on silica gel eluting with 15% ether in n-pentane afforded 126 (500.83 mg; 30% yield), 130 (333.89 mg; 20% yield), 133 (530.16 mg; 25% yield) and a fourth fraction enriched (~20%) in 129. The spectral data of compounds 130 and 133 are reported below.

6-Carbomethoxy-10-methylbicyclo[5.3.0]dec-10-en-2-one (130): m.p. 42-43°C (n-hexane at -20°C); ir ($CHCl_3$) 1730 (ester), 1670 (α,β-unsaturated ketone) and 1610 cm^{-1} (C=C, conjugated to ketone); pmr ($CDCl_3$) δ 3.6 (s, 3H, $-COOCH_3$), 2.10 (s, 3H, $CH_3-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$) and 1.5-3.6 (m, 12H); ms M^+ 222.1263 (calcd. for $C_{13}H_{18}O_3$: 222.1268). Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.27, H 3.11, O 21.62. Found: C 69.99, H 8.22, O 21.03.

10-Acetoxy-6-carbomethoxy-10-methylbicyclo[5.3.0]decan-

2-one (133): ir ($CHCl_3$) 1700 (ketone and 1735 (ester); pmr ($CDCl_3$) δ 1.35, 1.5 (both s, 3H total, CH_3-$\overset{|}{C}$(OAc)-) and 2.0, 2.05 (both s, 3H total, CH_3-COO-); ms m/e (M-60) 222.1256 (calcd. for $C_{13}H_{18}O_3$: 222.1258). The spectral data of 126 has already been discussed (vide supra).

6-Carbomethoxy-10-methylbicyclo[5.3.0]dec-10-en -2-one (126) and (130) from 133.

To a solution of 133 (500.0 mg, 1.77 mmol) in methanol (60 ml) was added 2N methanolic sodium methoxide (10 ml). The reaction mixture was stirred at room temperature for 4 hr, cooled to 0°C and acidified with 1N aqueous hydrochloric acid. The resulting solution was extracted with ether (2 x 100 ml). The ethereal layers were washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to afford an oily product. Purification of the oily product by column chromatography on silica gel eluting with 10% ether in n-pentane afforded 126 (236.17 mg; 60% yield) and 130 (157.18 mg; 40% yield). The spectral data of 126 and 130 have already been discussed (vide supra).

7-Acetoxy-1-carbomethoxy-3-hydroxy-3-methyltricyclo-[5.3.0.$0^{2,6}$]decane (134).

A solution of the keto-diester 102 (100.0 mg, 0.376 mmol)

in 15 ml of ether was stirred under a nitrogen atmosphere at -78°C and methyllithium (0.20 ml of 2.0M solution in ether, 0.40 mmol) was slowly added. The reaction mixture was stirred at -78°C for 2 hr and then poured into 10 ml of saturated ammonium chloride solution and the ethereal layer separated. The aqueous layer was extracted with ether (20 ml) and the combined ethereal solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residue on silica gel eluting with 15% ether in n-hexane afforded 134 995.43 mg; 90% yield): ir ($CHCl_3$) 3500 (OH), 1725 and 1730 cm^{-1} (esters); pmr ($CDCl_3$) δ 3.64 (s, 3H, $-COOCH_3$), 5.15 (s, 1H, -O-H), 1.92 (s, 3H, CH_3-COO-), 1.15 (s, 3H, CH_3-C(OH)-) and 1.5-2.7 (m, 12H); ms m/e (M-60) 222.1256 (calcd. for $C_{13}H_{18}O_3$: 222.1256).

5-Acetoxy-1-methyl-11-oxa-10-oxotetracyclo[7.2.1.0.^{5,9}0^{4,12}]-dodecane (135).

A solution of the keto-diester 102 (500.0 mg, 1.88 mmol) in ether (75 ml) was stirred under a nitrogen atmosphere at -78°C and methyllithium (1.035 ml of 2.0M solution in ether, 2.07 mmol) was added slowly. The reaction mixture was stirred at -78°C for 2 hr and then poured into 50 ml of ice-cold saturated ammonium chloride solution and the ethereal layer separated. The aqueous layer was extracted with ether (100 ml) and the combined ethereal solution was dried with

anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Purification of the residue by column chromatography eluting with 20% ether in n-hexane afforded 135 (399.44 mg; 85% yield). Crystallization from n-hexane-ether solution gave crystalline 135, m.p. 111-112°C; ir ($CHCl_3$) 1750 (γ-lactone) and 1730 cm^{-1} (ester); pmr ($CDCl_3$) δ 2.3 (d, 1H, J = 9 Hz, C-12 methine proton), 1.5 (s, 3H, C-1 methyl protons), 2.02 (s, 3H, CH_3-COO-), and 1.6-3.2 (m, 11H); ms M^+ 250.1206 (calcd. for $C_{14}H_{18}O_4$: 250.1204). Anal. Calcd. for $C_{14}H_{18}O_4$: C 67.17, H 7.31, O 25.61. Found: C 67.2, H 7.2, O 25.6.

1-Methyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecan-5-one

136 and 137.

To a stirred solution of 135 (1.0 g, 3.94 mmol) in methanol (18 ml) at room temperature was added 2N methanolic sodium methoxide (2 ml). The resulting reaction mixture was stirred at room temperature for 1 hr, then cooled in an ice-water bath and acidified with 1N aqueous hydrochloric acid and the product extracted with chloroform (3 x 40 ml). The organic layers were washed with water, combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to afford an oily residue. Purification of the residue by column chromatography eluting with 30% ether in n-hexane afforded a mixture of stereo-isomers 136 and 137 (9:1) respectively in 100% total yield.

Repeated flash chromatography of this mixture on silica gel eluting with 35% ethyl acetate in petroleum ether (30-60°C) afforded 136 (680.69 mg; 87.52% yield) and 137 (77.85 mg; 10% yield). When the reaction was allowed to proceed for 4 hr compounds 136 and 137 were obtained in a ratio of 1:1 and in a total yield of 98%.

Crystallization of 136 from n-hexane-ether solution afforded crystalline 136: m.p. 124-125°C; ir ($CHCl_3$) 1700 (ketone) and 1760 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 1.48 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.5 (t, 1H, J = 6 Hz, C-12 methine proton), 3.14 (m, 2H, C-4 and C-9 methine protons) and 1.5-2.7 (m, 10H); ms M^+ 208.1101 (calcd. for $C_{12}H_{16}O_3$: 208.1101). Anal. Calcd. for $C_{12}H_{16}O_3$: C 69.23, H 7.69. Found: C 69.03, H 7.66.

Crystallization of 137 from n-hexane-ether solution afforded crystalline 137: m.p. 130°C; ir ($CHCl_3$) 1700 (ketone) and 1755 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 1.52 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.48 (dd, 1H, J = 6 Hz, J' = 10 Hz, C-12 methine), 3.14 (m, 2H, C-4 and C-9 methine protons) and 1.6-2.4 (m, 10H); ms M^+ 208.1098 (calcd. for $C_{12}H_{16}O_3$: 208.1101). Anal. Calcd. for $C_{12}H_{16}O_3$: C 69.23, H 7.69. Found: C 69.03, H 7.66.

1,7-Dimethyl-3-methylthioethylenethio-11-oxatricyclo-[5.3.1.$0^{2,6}$]dec-2-ene (138).

A solution of lithium dimethyl cuprate (323.154 mg,

3.784 mmol) was prepared by the addition of methyllithium 7.533 mmol) in 4 ml of ether to a stirred suspension of cuprous iodide (720.35 mg, 3.784 mmol) in ether (22.5 ml) under a nitrogen atmosphere at -10°C. The reaction mixture was stirred at this temperature for 30 min. and a solution of the unsaturated ketone 119 (316.85 mg, 1.182 mmol) in ether 2 (ml) was added. The mixture was stirred at -10°C for 1 hr. It was then poured into ice-cold saturated ammonium chloride - 2N aqueous hydrochloric acid (1:1) solution with vigorous stirring and extracted with chloroform (2 x 50 ml). The chloroform layers were washed with water, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residual product on silica gel eluting with 5% ether in n-hexane afforded 138 (209.25 mg; 62.32% yield): ir ($CHCl_3$) 1600 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.25 (s, 3H, $\underline{CH_3}$-S-), 2.88-3.0 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-) and 1.28 (s, 6H, two $\underline{CH_3}$-$\overset{|}{\underset{|}{C}}$-O-).

6-Methylene-10-methoxy-10-methylthioethylenethio[5.3.0]-decan-2-one (144).

To a solution of 119 (63.37 mg, 0.236 mmol) in dry methanol (2 ml) under a nitrogen atmosphere was added sodium hydride (11.308 mg, 0.473 mmol) with stirring. There was no reaction at room temperature after 24 hr. The reaction mixture was heated to reflux for 18 hr, allowed to cool and

water (20 ml) was added. The product was extracted with chloroform (2 x 20 ml). The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Purification of the product by column chromatography on silica gel eluting with 15% ether in n-pentane gave 144 (65.20 mg; 98.4% yield): ir ($CHCl_3$) 1700 (saturated ketone) and 1640 cm^{-1} (C=C); pmr $CDCl_3$) 4.85 (s, 2H, $=CH_2$), 4.1 (s, 3H, $-O-CH_3$), 2.1 (s, 3H, CH_3S-) and 2.85 (s, 4H, $-S-CH_2-CH_2-S-$); ms M^+ 300.1462 (calcd. for $C_{15}H_{24}O_2S_2$: 300.1464).

6-Methylene-10-methylthioethylenethiobicyclo[5.3.0]deca-2,9-diene (148).

To a solution of the ketone 119 (38.0 mg, 0.143 mmol) in ether (2 ml) at -10°C under a nitrogen atmosphere was added lithium aluminum hydride (9.0 mg, 0.237 mmol) and the reaction mixture was stirred at -10°C for 0.5 hr. Water (0.2 ml) was added and stirred and anhydrous sodium sulfate was added to remove excess water. The mixture was filtered and the filtrate concentrated. Purification of the product by column chromatography on silica gel eluting with 5% ether in n-hexane afforded 148 (26.0 mg; 72.77% yield) and only a trace amount of 145.

In another experiment, the ketone 119 (38.0 mg, 0.143 mmol) was dissolved in dry methanol (2 ml). Sodium borohydride (18.03 mg, 0.477 mmol) was added and the reaction

mixture stirred at 0°C for 20 min. Water (1 ml) was added slowly followed by addition of aqueous ammonium chloride. The product was extracted with chloroform and the chloroform solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Purification as before afforded 148 (28.59 mg; 81.69% yield) as the only product: ir ($CHCl_3$) 1645 cm^{-1} (C=C); pmr ($CDCl_3$) δ 5.88 (t, 1H, J = 2 Hz, =CH-CH_2-), 5.78 (m, 1H, C-2 vinylic proton), 5.80 (d, 2H, J = 12 Hz, =CH_2), 2.7 (m, 4H, -S-CH_2-CH_2-S-), 3.75 (m, 1H, methine proton) and 2.18 (s, 3H, CH_3-S-); ms M^+ 252.1009 (calcd. for $C_{14}H_{20}S_2$: 252.1012).

Reduction of 119 and acetylation of the intermediate alkoxide.

To a solution of 119 (72.9 mg, 0.272 mmol) in ether (4 ml) at -10°C under a nitrogen atmosphere was added lithium aluminum hydride (15.0 mg, 0.395 mmol). The reaction mixture was stirred for 30 min. The reaction was monitored by thin layer chromatography to have gone to completion. Acetyl chloride (0.4 ml, 5.605 mmol) was added slowly. The reaction mixture was stirred for another 30 min. and ether (10 ml) was added. Water (1.0 ml) was added and stirred and the excess water removed by addition of anhydrous sodium sulfate. Filtration of the mixture and evaporation of the solvent afforded 149 (84.86 mg; ~100% crude yield). Thin layer chromatography analysis showed

that only this product was present. Purification by column chromatography on silica gel eluting with 5% ether in n-pentane resulted in the formation of 148 (50.92 mg; 60% 60% yield), 150 (8.49 mg; 10% yield) and isolation of 149 (20.56 mg; 30% yield).

In another similar reaction purification of the crude product by column chromatography on neutral alumina grade II eluting with 7% ether in n-pentane afforded 149 (50.92 mg; 60% yield) and 148 (27.41 mg; 40% yield).

2-Acetoxy-6-methylene-10-methylthioethylenethiobicyclo-[5.3.0]dec-10-ene (149): ir ($CHCl_3$) 1725 (ester) and 1640 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.1 (s, 3H, CH_3-COO-), 2.15 (s, 3H, CH_3-S-), 4.8 (s, 2H, $=CH_2$), 3.58 (t, 1H, J = 9 Hz, C-7 methine proton), 5.05 (t, 1H, J = 6 Hz, allylic C-2 proton), 2.6 (m, 4H, -S-CH_2-CH_2-S-) and 2.9 (m, 4H, allylic -CH_2-); ms M^+ 312.1201 (calcd. for $C_{16}H_{24}O_2S_2$: 312.1214).

10-Acetoxy-6-methylene-10-methylthioethylenethiobicyclo-[5.3.0]dec-1-ene (150): ir ($CHCl_3$) 1725 (ester) and 1635 cm^{-1} (C=C); pmr ($CDCl_3$) δ 4.75 (br. s, 2H, $=CH_2$), 4.6 (t, 1H, J < 1 Hz, =CH-CH_2-), 2.16 (s, 3H, CH_3-S-) and 2.04 (s, 3H, CH_3-COO-); ms M^+ 312.1201 (calcd. for $C_{16}H_{24}O_2S_2$: 312:1214).

6-Methylenebicyclo[5.3.0]dec-1-en-10-one (146) and 6-methyl-10-oxobicyclo[5.3.0]-1,6-decadiene (151).

To a solution of 149 (35.0 mg, 0.112 mmol) in 4 ml of acetonitrile-water (3:1) mixture was added mercuric chloride (152.0 mg; 0.56 mmol). The reaction mixture was stirred at room temperature for 2 hr and filtered. The filtrate was diluted with water (10 ml) and extracted with chloroform (2 x 30 ml). The chloroform layers were washed with saturated ammonium acetate solution and water, dried with anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the product on silica gel eluting with 5% ether in n-hexane afforded 146 (11.49 mg; 63.3% yield) and 151 (5.87 mg; 20% yield).

When 150 (35.0 mg, 0.112 mmol) was similarly treated it afforded the same product mixture. 146: ir ($CHCl_3$) 1715 (conjugated ketone) and 1645 cm^{-1} (C=C); pmr ($CDCl_3$) δ 4.82 (m, 2H, $=CH_2$), 6.8 (m, 1H, $-\underline{CH}=\overset{|}{C}-\overset{|}{C}=O$) and 3.5 (m, 1H, $=\overset{|}{C}-\underline{CH}-\overset{|}{C}=$); ms M^+ 162.1043 (calcd. for $C_{11}H_{14}O$: 162.1044). 151: ir ($CHCl_3$) 1690 (conjugated ketone) and 1650 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.1 (s, 3H, $\underline{CH_3}-\overset{|}{C}=$), 5.2 (m, 1H, $=\underline{CH}-$) and 1.5-3.5 (m, 10H); ms M^+ 162.1043 (calcd. for $C_{11}H_{14}O$: 162.1044).

Hydrolysis of 119.

(a) When 119 was treated with mercuric chloride as above and the reaction mixture heated to 50°C for 1 hr it

afforded 146 as the only product in 20% yield.

(b) To a solution of 119 (126.0 mg; 0.5 mmol) in 10 ml of acetonitrile was added titanium tetrachloride (189.73 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 20 min. and water (0.004 ml) was added. The mixture was stirred for 4 hr, poured into cold water and extracted with ether (2 x 20 ml). The ethereal layers were washed with saturated sodium chloride solution, combined, dried with anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the product of on silica gel eluting with 5% ether in n-hexane afforded 151 (80.10 mg, 100% yield). The spectral data of 151 has already been presented (vide supra).

3,3-Ethylenedithio-7-methyl-11-oxatricyclo[5.3.1.$0^{2,6}$]decane (153).

To a solution of the ketone 109 (50.0 mg, 0.197 mmol) in dry methanol (5 ml) was added sodium borohydride (25.0 mg; 0.669 mmol). The mixture was stirred at 0°C under a nitrogen atmosphere for 30 min. Water (1 ml) was added followed by addition of ammonium chloride. The organic product was extracted with ether (2 x 20 ml) and the ethereal layers washed with brine solution, combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to afford 153 (50.39 mg; ~100% yield); pmr ($CDCl_3$) δ 1.16 (s, 3H, -O-$\underset{|}{C}$-CH_3), 4.40 (m, 1H, -O-$\underline{CH}$-),

3.25 (br. s, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-) and 1.2-3.0 (m, 12H); ms M^+ 256.1202 (calcd. for $C_{13}H_{20}OS_2$: 256.1240).

Reduction of 109 with lithium aluminum hydride under standard conditions also afforded 153 in quantitative yield.

7-Methyl-11-oxatricyclo[5.3.1.$0^{2,6}$]decan-3-one (154).

To a solution of the thioketal 153 (251.97 mg, 0.984 mmol) in 20 ml of acetonitrile-water (3:1) was added mercuric chloride (1.3288 g, 4.894 mmol). The reaction mixture was stirred at room temperature for 12 hr and the solid residue filtered off. The filtrate was diluted with water (20 ml) and extracted with chloroform (2 x 25 ml). The organic layers were washed with saturated ammonium acetate solution and water, dried with anhydrous magnesium sulfate, filtered and concentrated. Column chromatography of the crude product on silica gel eluting with 10% ether in n-hexane afforded 154 (170.48 mg; 95.48% yield): ir ($CHCl_3$) 1740 cm^{-1} (ketone); pmr ($CDCl_3$) δ 1.32 (s, 3H, $\underline{CH_3}$-$\underset{|}{\overset{|}{C}}$-O-), 4.38 (br. s, 1H, -O-$\underline{\underset{|}{\overset{|}{C}}H}$-) and 1.25-2.8 (m, 12H); ms M^+ 180.1112 (calcd. for $C_{11}H_{16}O_2$: 180.1140).

6-Methylenebicyclo[5.3.0]dec-1-en-10-one (146) from 154.

A slurry of acetyl chloride (1.0 ml, 109.9 mg. 1.40 mmol) in pyridine (2 ml) was stirred at room temperature for 5 min. and a solution of 154 (30.0 mg, 0.167 mmol) in pyridine (1 ml) was added. The reaction mixture was

stirred for 40 hr, cooled in an ice bath and water (1 ml) was added slowly. The product was extracted with ether (2 x 20 ml), washed with 1N aqueous hydrochloric acid and brine solution. Flash evaporation of the solvent afforded an oily residue. To this residue was added 2N methanolic sodium hydroxide (1 ml). The mixture was stirred at room temperature for 4 hr, acidified with 10% aqueous hydrochloric acid and extracted with ether. The ethereal layer was washed with brine solution, dried with anhydrous magnesium sulfate, filtered and concentrated. Purification of the crude product by column chromatography on silica gel eluting with 10% ether in n-hexane afforded 146 (12.15 mg; 45% yield). The spectral data of 146 has already been discussed (vide supra).

10-Hydroxy-10-methyl-6-methylenebicyclo[5.3.0]dec-1-ene (147).

To a solution of 146 (35.0 mg, 0.216 mmol) in dry ether (5 ml) at -5°C was added methyllithium (0.422 mmol). The solution was stirred at -5°C under a nitrogen atmosphere for 30 min. Ether (15 ml) and saturated aqueous ammonium chloride (0.4 ml) were added. The ethereal solution was dried with anhydrous sodium sulfate, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel eluting with 10% ether in n-hexane to afford 147 as a 1:1 mixture of two epimers in a total of 95.83% yield (36.86 mg): ir ($CHCl_3$) 3500 (OH) and 1640 cm^{-1}

(C=C); pmr ($CDCl_3$) δ 5.75 (br. s, -O-H), 4.7 (m, 3H, vinylic protons) and 1.22, 1.24 (both s, 3H total, CH_3-); ms M^+ 164.0057 (calcd. for $C_{11}H_{16}O$: 164.0058).

10-Methyl-6-methylenebicyclo[5.3.0]dec-10-ene-2-one (139).

To a slurry of pyridinium chlorochromate (49.51 mg, 0.2296 mmol) in methylene chloride (6 ml) stirred at room temperature, was added a solution of the epimeric mixture of 147 (20.44 mg, 0.115 mmol) in methylene chloride (1 ml). The reaction mixture was stirred for 2 hr and diluted with ether (9 ml). The ether solution was decanted. The residue was washed with ether (3 x 20 ml) and the organic solutions decanted each time. The combined ethereal solution was washed with 5% aqueous sodium hydroxide solution (2 x 10 ml), 5% aqueous hydrochloric acid (2 x 10 ml), saturated aqueous sodium bicarbonate (2 x 10 ml) and dried with anhydrous sodium sulfate. Filtration and evaporation of the solvent afforded 139 (4.08 mg; 20% yield): ir ($CHCl_3$) 1670 (ketone) and 1605 cm^{-1} (C=C); pmr ($CDCl_3$) δ 4.76 (s, 2H, $=CH_2$), 2.04 (s, 3H, CH_3-C=C-C=O), 3.5 (br. m, 1H, allylic methine proton) and 1.5-2.8 (m, 10H), ms M^+ 164.0056 (calcd. for $C_{11}H_{16}O$: 164.0112).

6-Carbomethoxy-2,2-ethylenedithio-10-methylbicyclo[5.3.0]-dec-10-ene (160 and 161) and 6-carbomethoxy-2,2-ethylene-dithio-10-mercaptoethylenethio-10-methylbicyclo[5.3.0]-decane (162 and 163).

To a solution of the ketone 126 (1.40 g, 6.31 mmol) in methylene chloride (100 ml) maintained at -15°C were added 1,2-ethanedithiol (2.64 ml, 2.97 g, 31.60 mmol) and boron trifluoride etherate (1.95 ml, 15.78 mmol). The resulting solution was stirred at -15°C for 72 hr. The product mixture was poured into ice-cold 4N aqueous sodium hydroxide solution (40 ml) and the organic layer separated. The sodium hydroxide layer was extracted with chloroform (2 x 50 ml). The organic layers were washed with cold 4N aqueous sodium hydroxide (2 x 40 ml) and water, combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the product on silica gel eluting with 5% ether in n-hexane afforded 161 (1.51 g; 80% yield) and 162 (494.70 mg; 20% yield).

In another experiment, treatment of the ketone 130 with 1,2-ethanedithiol and boron trifluoride etherate under similar conditions afforded the thioketals 160 and 163 in 70% and 20% yields respectively. The spectral data of these compounds are presented below:

160: ir ($CHCl_3$) 1730 cm^{-1} (ester), pmr ($CDCl_3$) δ 1.98 (s, 3H, CH_3-C=), 3.62 (s, 3H, -$COOCH_3$) and 3.2-3.5 (m, 4H, -S-CH_2-CH_2-S-); ms M^+ 298.1052 (calcd. for $C_{15}H_{22}O_2S_2$: 298.1058). Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C 60.4, H 7.38, O 10.74, S 21.48. Found: C 60.55, H 7.5, O 10.88, S 21.44.

161: ir ($CHCl_3$) 1730 cm^{-1} (ester); pmr ($CDCl_3$) δ 3.65 (s, 3H, -$COOCH_3$), 2.02 (s, 3H, CH_3-C=) and 3.1-3.5 (m, 4H, -S-CH_2-CH_2-S-); ms M^+ 298.1052 (calcd. for $C_{15}H_{22}O_2S_2$: 298.1058). Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C 60.40, H 7.38, O 10.74, S 21.48. Found: C 60.39, H 7.53, O 11.04, S 21.85.

162: ir ($CHCl_3$) 1725 (ester); pmr ($CDCl_3$) δ 1.7 (s, 3H, CH_3-C(-S-)), 3.67 (s, 3H, -$COOCH_3$), 3.2-3.5 (m, 4H, -S-CH_2-CH_2-S-), 2.6-2.9 (m, 4H, -S-CH_2-CH_2-S-) and 1.2-2.6 (m, 14H); ms M^+ 392.0972 (calcd. for $C_{17}H_{28}O_2S_4$: 392.0979).

163: ir ($CHCl_3$) 1725 cm^{-1} (ester); pmr ($CDCl_3$) δ 1.74 (s, 3H, CH_3-C(-S-)), 3.22-3.5 (m, 4H, -S-CH_2-CH_2-S-) and 1.2-3.0 (m, 18H); ms M^+ 392.0972 (calcd. for $C_{17}H_{28}O_2S_4$: 392.0979).

2,2-Ethylenedithio-6-hydroxymethyl-10-methylbicyclo[5.3.0]-decane (164) and (165).

A suspension of lithium aluminum hydride (583.32 mg, 15.35 mmol) in anhydrous ether (50 ml) was stirred at 0°C

under a nitrogen atmosphere and a solution of the ester 161 (1.50 g, 5.03 mmol) in ether (25 ml) was added slowly. The resulting mixture was stirred at 0°C for 1.5 hr. Water (1 ml) was added and the ethereal solution was dried with anhydrous sodium sulfate. The solid residue was filtered off and washed with ether. The solvent was evaporated and the oily product purified by column chromatography. Elution with 15% ether in n-hexane afforded 164 (1.29 g, 15% yield): ir ($CHCl_3$) 3450 (OH) and 1670 cm^{-1} (C=C); pmr ($CDCl_3$) δ 1.96 (s, 3H, $\underline{CH_3}$-C=), 3.0-3.45 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), 3.45-3.6 (m, 2H, -O-$\underline{CH_2}$-) and 1.3-3.0 (m, 13H); ms M^+ 270.1111 (calcd. for $C_{14}H_{22}OS_2$: 270.1065).

Similarly, reduction of 160 (1.5 g, 5.03 mmol) afforded 165 (1.20 g; 94.5% yield): ir ($CHCl_3$) 3606 and 3450 cm^{-1} (OH); pmr ($CDCl_3$) δ 1.98 (s, 3H, $\underline{CH_3}$-C=), 3.45-3.7 (m, 4H, -O-$\underline{CH_2}$-), 3.0-3.4 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-) and 1.3-3.0 (m, 13H); ms M^+ 270.1111 (calcd. for $C_{14}H_{20}OS_2$: 270.1065).

2,2-Ethylenedithio-10-methyl-6-p-toluenesulfonyloxymethylbicyclo[5.3.0]dec-10-ene (166 and 167).

A solution of 164 (1.20 g, 4.44 mmol) in pyridine (40 ml) was stirred at 0°C and p-toluenesulfonyl chloride (1.69 g, 8.88 mmol) in pyridine (20 ml) was added. The resulting solution was stirred at -10°C for 36 hr. The product was poured into ice-water mixture (100 ml) with stirring and extracted with ether (2 x 100 ml). The ethereal

layers were washed with cold 1N aqueous hydrochloric acid (50 ml) and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to afford a solid residue. Purification of the crude product by column chromatography on silica gel eluting with 15% ether in n-hexane followed by crystallization from n-hexane-ether solution afforded 166 (1.79 g; 95% yield): m.p. 99-100°C; pmr ($CDCl_3$) δ 7.35, 7.8 (both d, 2H each, J = 8 Hz each, aromatic protons), 4.05 (d, 2H, J = 6 Hz, $-\underline{CH_2}-O-$), 3.2-3.6 (m, 4H, $-S-\underline{CH_2}-\underline{CH_2}-S-$), 2.46 (s, 3H, $\underline{CH_3}-C_6H_4-$), 2.0 (s, 3H, $\underline{CH_3}-\dot{C}=$) and 1.3-3.2 (m, 12H); ms M^+ 424.1205 (calcd. for $C_{21}H_{28}O_3S_3$: 424.1212). Anal. Calcd. for $C_{21}H_{28}O_3S_3$: C 59.43, H 6.6, O 11.32, S 22.64. Found: C 59.57, H 6.65, O 11.01, S 22.30.

Similarly, treatment of 165 (1.2 g, 4.44 mmol) with p-toluenesulfonyl chloride in pyridine afforded the isomeric p-toluenesulfonate 167 (1.79 g, 95% yield): m.p. 88-89°C (n-hexane-ether); pmr ($CDCl_3$) δ 1.90 (s, 3H, $\underline{CH_3}-\dot{C}=$), 3.1-3.6 (m, 4H, $-S-\underline{CH_2}-\underline{CH_2}-S-$), 3.9 (d, 2H, J = 6 Hz, $-\underline{CH_2}-O-$), 7.34, 7.78 (both d, 2H each, J = 8 Hz each, aromatic protons, 2.42 (s, 3H, $\underline{CH_3}-C_6H_4-$) and 1.2-3.1 (m, 12H); ms M^+ 424.1205 (calcd. for $C_{21}H_{28}O_3S_3$: 424.1212). Anal. Calcd. for $C_{21}H_{28}O_3S_3$: C 59.43, H 6.60, O 11.32, S 22.64. Found: C 59.60, H 6.71, O 11.21, S 22.40.

2,2-Ethylenedithio-6,10-dimethylbicyclo[5.3.0]dec-10-ene (168 and 169).

A suspension of lithium aluminum hydride (506.76 mg, 13.34 mmol) in anhydrous ether (60 ml) was stirred at 0°C under a nitrogen atmosphere and a solution of the sulfonate 166 (1.70 g, 4.01 mmol) in ether (40 ml) was added. The resulting mixture was allowed to warm to room temperature and stirred for 3 hr. The excess lithium aluminum hydride was slowly decomposed with water (1 ml) and anhydrous sodium sulfate was added to dry the ethereal solution. The solid residue was filtered off and washed with ether. The solvent was removed by flash evaporation to afford an oily product which upon purification by column chromatography eluting with 2% ether in n-hexane afforded 168 (875.81 mg; 86% yield): pmr ($CDCl_3$) δ 1.98 (s, 3H, $\underline{CH_3}$-C=), 3.1-3.6 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), 0.96 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-) and 1.2-3.1 (m, 12H); ms M^+ 254.1164 (calcd. for $C_{14}H_{22}S_2$: 254.1166).

Similarly, reductive cleavage of the toluenesulfonate 167 (850.0 mg, 2.005 mmol) afforded 435.21 mg of 169; 85% yield; pmr ($CDCl_3$) δ 1.97 (s, 3H, $\underline{CH_3}$-C=), 3.2-3.6 (m, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), 0.76 (d, 3H, J = 6 Hz, $\underline{CH_3}$-CH-) and 1.15-3.0 (m, 12H); ms M^+ 254.1164 (calcd. for $C_{14}H_{22}S_2$: 254.1166).

6,10-Dimethylbicyclo[5.3.0]dec-10-en-2-one (131 and 132).

A solution of mercuric chloride (4.51 g, 16.61 mmol) in 45 ml of acetonitrile-water (2:1) was stirred at room temperature and a solution of the thioketal 168 (842.50 mg, 3.32 mmol) in 30 ml of acetonitrile-ether (1:1) was added. After 3 hr, the reaction mixture was filtered to remove solid residues. The filtrate was diluted with water (40 ml) and extracted with ether (100 ml). The ethereal extract was washed with saturated aqueous ammonium acetate solution (2 x 50 ml) and water, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to afford an oily residue. Purification by column chromatography on silica gel eluting with 5% ether in n-hexane afforded 131 (442.81 mg; 75% yield): ir ($CHCl_3$) 1680 (α,β-unsaturated ketone) and 1610 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.02 (s, 3H, $\underline{CH_3}$-C=), 0.96 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-) and 1.2-2.7 (m, 12H); ms M^+ 178.1359 (calcd. for $C_{12}H_{18}O$: 178.1362).

Similarly, hydrolysis of 169 (421.25 mg, 1.66 mmol) ~~of 169~~ with mercuric chloride afforded 132 (221.45 mg; 75% yield): ir ($CHCl_3$) 1680 (α,β-unsaturated ketone) and 1610 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.08 (s, 3H, $\underline{CH_3}$-C=), 0.77 (d, 3H, J = 6 Hz, $\underline{CH_3}$-CH-) and 1.3-2.6 (m, 11H); ms M^+ 178.1359 (calcd. for $C_{12}H_{18}O$: 178.1362).

6,10-Dimethyl-2-ethynylbicyclo[5.3.0]dec-1o-ene-2-ol (140 and 179) and 6,10-Dimethyl-2,10-diethynylbicyclo[5.3.0]-decan-2-ol(173).

In a 100 ml three-necked flask equiped with a magnetic stirrer, a dry ice condenser, a gas inlet tube and a serum cap and flushed with dry nitrogen was placed 50 ml of freshly distilled tetrahydrofuran. The flask was cooled to -78°C. Excess acetylene was added by bubbling acetylene into the tetrahydrofuran through two cooled (-78°C) traps containing concentrated sulfuric acid and soda lime (4-8 mesh). To this solution n-butyllithium (13.62 mmol, 6 ml of 2.27M solution in n-hexane) was added slowly over a 10 min. period. The resulting solution was stirred for a further 10 min. and a solution of the ketone 131 (504.25 mg, 2.83 mmol) in THF (50 ml) was added slowly by means of a hypodermic syringe. The reaction mixture was maintained between -78°C and -55°C for 1 hr, cooled to -78°C and allowed to warm to -35°C during 1 hr period, maintained between -35°C to -45°C for 30 min. and finally allowed to warm from -45°C to 10°C. The temperature control was crucial for reproducible maximum yield and complete conversion of 131 into products. Water (3 ml) was added until the aqueous layer became pasty and the organic layer was decanted. The aqueous pasty layer was washed with ether (2 x 50 ml). The combined organic solution was dried with

anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the crude product on silica gel eluting with 2% ether in n-pentane afforded 140 (392.98 mg; 68% yield) and 173 (196.97 mg; 30% yield).

140: ir ($CHCl_3$) 3610 (OH) and 3315 cm^{-1} (≡C-H); pmr (CDl_3) δ 2.0 (s, 3H, $\underline{CH_3}$-C=), 2.46 (s, 1H, ≡C-H), 0.94 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 3.75 (br. s, 1H, -O-H) and 1.2-3.2 (m, 12H); ms M^+ 204.1516 (calcd. for $C_{14}H_{20}O$: 204.1505).

173: ir 3600 (OH) and 3315 cm^{-1} (≡C-H); pmr ($CDCl_3$) δ 2.44, 2.46 (both s, 1H each, C≡C-H) 3.6 (br. s, 1H, -O-H) and 1.2-3.0 (m, 13H); ms M^+ 230.1016 (calcd. for $C_{16}H_{22}O$: 230.1018).

The isomeric ketone 132 (220.40 mg; 1.61 mmol) was similarly treated with lithium acetylide to afford the ethynyl compound 179 (160.4 mg; 55% yield): ir ($CHCl_3$) 3600 (OH), 3315 cm^{-1} (≡C-H); pmr ($CDCl_3$) δ 2.46 (s, 1H, ≡C-H), 1.98 (s, 3H, $\underline{CH_3}$-C=), 0.80 (d, 3H, J = 7 Hz, $\underline{CH_3}$-CH-) and 1.3-2.7 (m, 12H); ms M^+ 204.1516 (calcd. for $C_{14}H_{20}O$: 204.1505).

2-Acetoxy-2-acetyl-6,10-dimethylbicyclo[5.3.0]dec-10-ene (172 and 180) and 1,5-dimethyl-12-thiotricyclo[7.3.1.$0^{4,13}$]tridec-9-en-10-one (174 and 181).

A solution of the ethynyl compound 140 (117.92 mg,

0.58 mmol) in dry ethyl acetate (30 ml) was stirred at room temperature and mercuric acetate (406.64 mg; 1.28 mmol) was added. The reaction mixture was stirred for 24 hr, cooled to 0°C and 2-methyl-2-propanethiol (0.16 ml, 124.86 mg, 1.39 mmol) was added. The mixture was stirred for 20 min. and filtered. The solid residue was washed with chloroform and the combined solution concentrated. Ether (40 ml) was added to the crude product and filtered again. The ether solution was concentrated and the residue purified by column chromatography on silica gel eluting with 10% ether in n-hexane to give 172 (76.30 mg; 50% yield) and 174 (41.07 mg; 30% yield).

172: ir ($CHCl_3$) 1735 (ester), 1720 (ketone) and 1610 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.12 (s, 3H, $\underline{CH_3}$-C(=O)-), 2.06 (s, 3H, $\underline{CH_3}$-COO-), 1.25 (s, 3H, $\underline{CH_3}$-C(=)-), 0.85 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-) and 1.2-3.2 (m, 12H); ms M^+ 164.1737 (calcd. for $C_{16}H_{24}O_3$: 264.1742).

174: ir ($CHCl_3$) 1700 (α,β-unsaturated ketone) and 1660 cm^{-1} (C=C); pmr ($CDCl_3$) δ 1.10 (s, 3H, $\underline{CH_3}$-C-S-), 2.35 (d, 2H, J = 4 Hz, -S-$\underline{CH_2}$-C(=O)-), 2.7-3.1 (m, 1H, =C-$\underline{CH}$-), 0.89 (d, 3H, J = 6 Hz, $\underline{CH_3}$-CH-) and 1.2-2.7 (m, 11H); ms M^+ 236.1242 (calcd. for $C_{11}H_{20}OS$: 236.1234).

By similar treatment 179 (117.92 mg, 0.58 mmol) afforded 180 (63.08 mg; 40% yield) and 181 (55.76 mg; 40% yield). 180: ir ($CHCl_3$) 1720 (ketone), 1735 (ester) and 1650 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.10 (s, 3H, $\underline{CH_3}$-C(=O)-), 2.04 (s, 3H, $\underline{CH_3}$-COO-), 0.85 (d, 3H, J = 7 Hz, $\underline{CH_3}$-CH-) and

1.7-3.2 (m, 12H); ms M^+ 264.1737 (calcd. for $C_{16}H_{24}O_3$: 264.1742).

181: ir ($CHCl_3$) 1700 (α,β-unsaturated ketone) and 1660 cm^{-1} (C=C); pmr ($CDCl_3$) δ 1.07 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-S-), 2.35 (d, 2H, J = 3 Hz, -S-$\underline{CH_2}$-$\overset{|}{C}$=O), 0.87 (d, 3H, J = 7 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 2.7-3.06 (m, 1H, allylic methine proton) and 1.2-2.6 (m, 11H); ms M^+ 236.1242 (calcd. for $C_{11}H_{20}OS$: 236.1234).

2-Acetyl-6,10-dimethylbicyclo[5.3.0]dec-10-en-2-ol (175).

A solution of the keto-ester 172 (70.0 mg, 0.27 mmol) in methanol (5 ml) was stirred at room temperature and 2N aqueous sodium hydroxide (1 ml) was added. The resulting solution was stirred at room temperature for 8 hr, acidified with 2N aqueous sulfuric acid and extracted with ether. The ethereal solution was washed with brine and dried with anhydrous sodium sulfate. Evaporation of the solvent afforded 175 (57.86 mg; 98.58% yield): ir ($CHCl_3$) 3480 (OH), 1665 (C=C) and 1710 cm^{-1} (ketone); pmr ($CDCl_3$) δ 1.26 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$=), 2.1 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$=O), 0.87 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 3.92 (br. s, 1H, -O-$\underline{H}$) and 1.5-3.0 (m, 12H); ms M^+ 222.1581 (calcd. for $C_{14}H_{22}O_2$: 222.1582).

6,10-Dimethyl-3-hydroxymethylenebicyclo[5.3.0]dec-10-en-2-one (182).

To a solution of the ketone 131 (792.45 mg, 4.452 mmol)

in 1,2-dimethoxyethane (40 ml) stirred at room temperature under a nitrogen atmosphere were added, 10 min. apart, lithium tert-butoxide (783.53 mg, 9.79 mmol) and ethyl formate (1.06 ml, 175.2 mg, 13.164 mmol). The mixture was stirred at room temperature for 18 hr and then heated to reflux gently for 6 hr. The resulting mixture was cooled in an ice-water bath, and acidified with 10% aqueous hydrochloric acid. The product was extracted with ether (2 x 50 ml), washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated. Flash chromatography of the crude product on silica gel eluting with 10% ethyl acetate in petroleum ether (30-60°C) afforded 182 (612.89 mg; 66.83% yield): ir ($CHCl_3$) 3500 (OH) and 1605 cm^{-1} (ketone); pmr ($CDCl_3$) δ 0.95 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 8.27 (d, 1H, J = 5 Hz, O=C-C=$\underline{CH}$($\underline{OH}$)), 15.48, 15.37 (both d, 1H total, J = 5 Hz each, O=C-C=CH-$\underline{OH}$), 2.01 (s, 3H, $\underline{CH_3}$-C=), 3.2 (br. s, 1H, C-1 allylic methine proton) and 1.2-2.8 (m, 9H); ms M^+ 206.1309 (calcd. for $C_{13}H_{18}O_2$: 206.1298).

6,10-Dimethyl-3,3-(propane-1,3-dithio)bicyclo[5.3.0]dec-10-en-2-one (183).

A solution of the hydroxymethylene ketone 182 (595.784 mg, 2.892 mmol) and propane-1,3-dithiol-p-toluenesulfonate (1.831 g, 4.401 mmol) in 98% absolute ethanol (40 ml) was warmed to 40°C and a solution of potassium

acetate (3.406 g, 34.76 mmol) in hot 98% ethanol (20 ml) was added. The resulting reaction mixture was heated under reflux for 24 hr, cooled, poured into saturated aqueous sodium chloride solution and extracted with ether (3 x 50 ml). The combined ethereal solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. The residual oily product was purified by column chromatography on neutral alumina grade I eluting with 10% ether in benzene to afford 183 (420.04 mg; 44.5% yield): ir ($CHCl_3$) 1665 (α,β-unsaturated ketone) and 1605 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.01 (s, 3H, $\underline{CH_3}$-C=), 0.96 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 3.0-3.8 (m, 4H, -S-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-S-) and 1.2-2.30 (m, 14H); ms M^+ 282.1108 (calcd. for $C_{15}H_{22}OS_2$: 282.110).

5-Methoxymethylene-1-methyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]-dodecane (187 and 188).

To a suspension of (methoxymethyl)-triphenylphosphonium chloride (6.59 g, 19.23 mmol) in dry tetrahydrofuran (80 ml) stirred at room temperature under a nitrogen atmosphere was added phenyllithium (18.75 mmol, 7.27 ml of 2.58M solution in benzene-ether (7:3)). The reaction mixture was stirred for 30 min. The resulting dark-red solution of methoxymethylenetriphenylphosphorane was cooled to -30°C and a solution of the ketone 136 (1.016 g, 4.81 mmol) in dry tetrahydrofuran (80 ml) was added slowly. The reaction

mixture was allowed to warm to room temperature and maintained at this temperature with stirring for 20 hr and then heated to reflux for 1 hr. The mixture was poured slowly into ice-water mixture and extracted with ether (3 x 100 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. The residual product was purified by column chromatography on silica gel eluting with 5% ether in n-hexane to remove triphenylphosphine oxide and then with 20% ether in n-hexane to afford the methyl vinyl ether 187 and 188 (908.671 mg: (5:1); 80% yield). Further chromatographic purification afforded 187. Crystallization from n-hexane-ether solution afforded crystalline 187: m.p. 104-105°C; ir ($CHCl_3$) 1675 (C=C) and 1760 cm^{-1} (γ-lactone); pmr (CCl_4) δ 5.65 (s, 1H, =CH-OCH_3), 3.5 (s, 3H, =CH-OCH_3), 3.4 (m, 2H, C-4 and C-9 methine protons), 1.4 (s, 3H, CH_3-C(CH$_3$)-O-), and 1.4-2.9 (m, 11H); ms M^+ 236.1411 (calcd. for $C_{14}H_{20}O_3$: 236.1416). Anal. Calcd. for $C_{14}H_{20}O_3$: C 71.19, H 8.47, O 20.34. Found: C 71.00, H 8.45, O 21.05.

Similarly when 137 (508.0 mg, 2.40 mmol) was treated with methoxymethylenetriphenylphosphorane an inseparable mixture of vinyl ethers 187 and 188 (1:5) in a total of 80% yield was obtained.

1-Methyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane-1-carboxyaldehyde (189 and 190).

To a solution of 187 (1.0 g, 4.2372 mmol) in distilled tetrahydrofuran (60 ml) at room temperature was added 6N aqueous hydrochloric acid (30 ml) with stirring. The resulting solution was stirred at room temperature for 4 hr. The product was extracted with ether 50 ml and chloroform (2 x 50 ml). The organic layers were washed with water, combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation to give a single product 189. Purification by column chromatography on silica gel eluting with 30% ether in n-hexane gave pure 189 (930.0 mg; ~100% yield): ir ($CHCl_3$) 1730 (aldehyde) and 1755 cm^{-1} (γ-lactone); pmr (CCl_4) δ 1.48 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 9.50 (br. s, 1H, -$\overset{|}{C}$H-C$\underline{H}$=O) and 1.2-3.0 (m, 14H); ms M^+ 222.1253 (calcd. for $C_{13}H_{18}O_3$: 222.1265).

Similar treatment of the mixture of vinyl ethers 187 and 188 obtained from both 136 and 137 afforded 189 and 190. Purification by column chromatography eluting with 25% ether in n-hexane afforded 189 and 190 (1:5 respectively from 137) and 1:1.23 respectively from the mixture of vinyl ethers from 136.

190: ir 1730 (aldehyde) and 1755 cm^{-1} (γ-lactone); pmr (CCl_4) δ 1.51 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 9.58 (br. s, 1H, -$\overset{|}{C}$H-C$\underline{H}$-O) and 1.2-3.2 (m, 14H); ms M^+ 222.1253 (calcd. for $C_{13}H_{18}O_3$: 222.1265).

5-Ethylenedithiomethyl-1-methyl-11-oxa-10-oxotricyclo-[7.2.1.$0^{4,12}$]dodecane (191 and 192).

A solution of 189 (1.039 g, 4.68 mmol) in methylene chloride (75 ml) was stirred at 0-5°C and 1,2-ethanedithiol (913.68 mg, 9.36 mmol) was added. To the resulting solution was added boron trifluoride etherate (0.4 ml) and the reaction mixture stirred at 0-5°C for 4 hr. The mixture was washed with water and the aqueous solution extracted with dichloromethane (50 ml). The combined organic solution was dried over anhydrous sodium sulfate, filtered and concentrated. The residual oil was purified by column chromatography on silica gel eluting with 10% ether in n-hexane to afford 191 (1.304 g; 93.54% yield) as the only product. Crystallization of 191 from ethanol afforded crystalline 191: m.p. 128.5-129.5°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 4.84 (d, 1H, J = 2 Hz, -S-CH-S-), 3.16 (s, 4H, -S-CH_2-CH_2-S-), 1.4 (s, 3H, CH_3-C-O-) and 1.2-2.8 (m, 14H); ms M^+ 298.1061 (calcd. for $C_{15}H_{22}O_2S_2$: 298.1061). Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C 60.4, H 7.38, O 10.74, S 21.48. Found: C 60.12, H 7.43, O 10.57, S 21.44.

Similarly, thioketalization of the aldehyde 190 (1.04 g, 4.685 mmol) afforded 192 (1.32 g; 95% yield). Crystallization from ethanol afforded crystalline 192: 134-135°C; ir ($CHCl_3$) 1755 (γ-lactone); pmr ($CDCl_3$) δ 4.76 (d, 1H, J = 3 Hz, -S-CH-S-), 1.46 (s, 3H, CH_3-C-O-), 3.2 (m, 4H,

-S-$\underline{CH_2}$-$\underline{CH_2}$-S-) and 1.2-2.8 (m, 14H); ms M^+ 298.1061 (calcd. for $C_{15}H_{22}O_2S_2$: 298.1061). Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C 60.4, H 7.38, O 10.74, S 21.48. Found: C 59.79, H 7.44, O 10.25, S 20.94.

1,5-Dimethyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane (193 and 194).

Approximately 7.0 g of freshly prepared Ra-Ni (W-2) was suspended in distilled benzene (40 ml) under a nitrogen atmosphere and a solution of the thioketal 191 (628.44 mg, 2.108 mmol) in benzene (40 ml) was added. The reaction mixture was stirred at room temperature for 4 hr and then diluted with ethanol (40 ml) and gravity filtered. The residue was repeatedly washed with benzene (5 x 50 ml). After flash evaporation of the solvent, the oily residue was purified by flash chromatography on silica gel eluting with 12% ethyl acetate in peteoleum ether (30-60°C) to afford an oily product 193 (368.30 mg; 84% yield): ir ($CHCl_3$) 1750 1750 cm^{-1} (γ-lactone); pmr (CCl_4) δ 0.89 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 1.37 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.48 (t, 1H, J = 6 Hz, C-12 methine proton), 2.90 (m, 1H, C-9 methine proton) and 1.1-2.5 (m, 12H); ms M^+ 208.1469 (calcd. for $C_{13}H_{20}O_2$: 208.1501). Anal. Calcd. for $C_{13}H_{20}O_2$: C 75.0, H 9.62, O 15.38. Found: C 74.7, H 9.58, O 5.11.

Similarly, reductive cleavage of the thioketal moiety of 192 (720.1 mg; 2.416 mmol) afforded an oily product 194

(427.23 mg; 85% yield). Crystallization from n-hexane afforded crystalline 194: m.p. 64-65°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr (CCl_4) δ 0.95 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.4 (s, 3H, $\underline{CH_3}$-C(-O-)) and 1.2-2.6 (m, 14H); ms M^+ 208.1469 (calcd. for $C_{13}H_{20}O_2$: 208.1501). Anal. Calcd. for $C_{13}H_{20}O_2$: C 75.0, H 9.62, O 15.38. Found: C 75.14, H 9.59, O 15.41.

1-Methyl-5-methylene-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane (197).

Methyltriphenylphosphonium bromide (6.654 g, 18.63 mmol) was suspended in dry tetrahydrofuran (100 ml) and n-butyllithium (17.4 mmol, 8.31 ml of 2.4M solution in n-hexane) was added slowly. The mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. To the resulting deep red solution, the keto-lactone 136 (906.0 mg, 4.36 mmol) in tetrahydrofuran (25 ml) was added slowly and the reaction mixture stirred at room temperature for 15 hr. It was then poured into ice-water mixture and extracted with ether (3 x 100 ml). The ethereal solutions were washed with saturated aqueous sodium chloride solution, combined dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with 5% ether in n-hexane and then with 10% ether in n-hexane to give 197 (43.10 mg; 60% yield). Crystallization from n-hexane afforded crystalline 197: m.p. 101-102°C; ir ($CHCl_3$) 1755 (γ-lactone) and 1650 cm^{-1} (C=C);

pmr (CCl_4) δ 4.64 (br. S, 2H, J < 1 Hz, $=CH_2$), 1.4 (s, 3H, CH_3-C(-O-)) and 1.3-3.1 (m, 13H); ms M^+ 206.1307 (calcd. for $C_{13}H_{18}O_2$: 206.1305). Anal. Calcd. for $C_{13}H_{18}O_2$: C 75.73, H 8.74, O 15.53. Found: C 75.34, H 8.54, O 15.62.

Spiro[1-methyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane-5-2'-oxirane] (198 and 199).

A solution of m-chloroperbenzoic acid 165.655 mg, 0.96 mmol) in methylene chloride (15 ml) was stirred at room temperature and a solution of the olefin 197 (140.84 mg, 0.68 mmol) in methylene chloride (5 ml) was added. The reaction mixture was stirred for 2 hr. Aqueous 10% sodium sulfite (2 ml) was added. After stirring for 5 min the mixture was poured into water and the organic products extracted with methylene chloride (2 x 25 ml). The organic solutions were washed with 10% aqueous sodium bicarbonate solution and water, combined, dried with anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by flash chromatography on silica gel eluting with 35% ethyl acetate in petroleum ether (30-60°C) afforded two oxiranes 198 (58.03 mg; 38.23% yield) and 199 (84.22 mg; 55.48% yield). Crystallization of 198 from n-hexane-ether solution afforded a crystalline material: m.p. 129-130°C; ir ($CHCl_3$) 1755 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 1.42 (s, 3H, CH_3-C(-O-)), 2.45, 2.76 (both d, 1H each, J = 5 Hz each, $-CH_2$-O-) and 1.2-2.3 (m, 13H); ms M^+ 222.1258 (calcd. for

$C_{13}H_{18}O_3$: 222.1247). Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11, O 21.62. Found: C 70.36, H 8.25, O 21.92.

Crystallization of 199 from n-hexane-ether solution afforded a crystalline compound: m.p. 123-124°C; ir ($CHCl_3$) 1755 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 1.42 (s, 3H, $\underline{CH_3}$-C(-O-)), 2.57, 2.76 (both d, 1H each, J = 5 Hz each, -O-$\underline{CH_2}$-) and 1.2-3.2 (m, 13H); ms M^+ 222.1258 (calcd. for $C_{13}H_{18}O_3$: 222.1247). Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11, O 21.62. Found: C 70.24, H 8.22, O 21.79.

1-Methyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane-5-carboxyaldehyde (200).

To a solution of 198 (50.0 mg, 0.225 mmol) in dry benzene (10 ml) at 0°C under a nitrogen atmosphere was added boron trifluoride etherate (0.2 ml). The resulting solution was stirred for 4 hr. The reaction was quenched with water and the mixture poured into 10% aqueous sodium bicarbonate solution and extracted with benzene (3 x 20 ml). The organic solutions were washed with 10% aqueous sodium bicarbonate solution and water, dried with anhydrous sodium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 30% ethyl acetate in petroleum ether (30-60°C) afforded the aldehyde 200 (48.0 mg, 96.0% yield): ir 1730 (aldehyde) and 1755 cm^{-1} (γ-lactone); pmr (CCl_4) δ 1.48 (s, 3H, $\underline{CH_3}$-C(-O-)), 9.5 (br. s, -CH-$\underline{CH}$=O) and 1.2-3.0 (m, 14H); ms M^+ 222.1253 (calcd. for $C_{13}H_{18}O_3$:

222.1264).

Similar treatment of the oxirane 199 (80.0 mg, 0.36 mmol) afforded the same aldehyde 200 (78.0 mg; 97.5% yield).

5-Ethylenedithiomethyl-1-methyl-11-oxa-10-oxotricyclo-[7.2.1.$0^{4,12}$]dodecane (201) from 200.

To a solution of the aldehyde 200 (70.0 mg, 0.315 mmol), obtained from the oxirane 199, in methylene chloride (15 ml) were added 1,2-ethanedithiol (0.05 ml, 54.63 mg, 0.634 mmol) and boron trifluoride etherate (0.1 ml). The reaction mixture was stirred at 0-5°C for 4 hr. The mixture was poured into water and extracted with methylene chloride (2 x 25 ml). The organic solutions were washed with water, combined, dried with anhydrous magnesium sulfate and the solvent removed by flash evaporation. Column chromatography of the crude product eluting with 5% ether in n-hexane and then 10% ether in n-hexane afforded a single thioketal 201 (79.87 mg; 85% yield). Crystallization from ethanol afforded crystalline 201: m.p. 128.5-129°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 4.84 (d, 1H, J = 2 Hz; -S-$\underline{CH}$-S-), 3.16 (s, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), 1.4 (s, 3H, $\underline{CH_3}$-$\underline{C}$-O) and 1.2-2.8 (m, 14H); ms M^+ 298.1061 (calcd. for $C_{15}H_{22}O_2S_2$: 298.1061).

The aldehyde obtained from the oxirane 198 (40.0 mg, 0.18 mmol) was similarly treated to afford the same single thioketal 201 (39.98 mg; 85% yield).

1,5-Dimethyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodecane (202) from 201.

To a suspension of Ra-Ni (W-2) (approximately 1.0 g) in dry benzene (10 ml) at room temperature under a nitrogen atmosphere was added a solution of the thioketal 201 (110.0 mg, 0.369 mmol) in benzene (10 ml). The reaction mixture was stirred for 4 hr and diluted with ethanol (10 ml) and gravity filtered. The residue was washed with benzene (3 x 10 ml) and the solvent removed by flash evaporation. Purification of the residue by flash chromatography on silica gel eluting with 12% ethyl acetate in petroleum ether (30-60°C) afforded 202 (66.01 mg; 86.1% yield): ir ($CHCl_3$) 1750 (γ-lactone); pmr (CCl_4) δ 0.89 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.37 (s, 3H, $\underline{CH_3}$-C-O-), 2.48 (t, 1H, J = 6 Hz, C-12 methine proton), 2.90 (m, 1H, C-9 methine proton) and 1.1-2.5 (m, 12H); ms M^+ 208.1069 (calcd. for $C_{13}H_{20}O_2$: 208.1045).

1,5,10-Trimethyl-11-oxa-$\Delta^{9,10}$tricyclo[7.2.1.$0^{4,12}$]dodecane (204).

A solution of the lactone 193 (475.0 mg, 2.284 mmol) in anhydrous ether (30 ml) was stirred at 0°C under a nitrogen atmosphere and methylmagnesium bromide (11.42 mmol, 11.42 ml of 1.0M solution in ether) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred

for 6 hr. The mixture was poured into ice-cold saturated aqueous ammonium chloride solution and extracted with ether (2 x 50 ml). The ethereal solutions were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and concentrated to 15 ml. To this solution d-10-camphorsulfonic acid (30 mg, 0.129 mmol) was added. After stirring at room temperature for 2 hr the mixture was poured into water and extracted with ether (2 x 25 ml). The ethereal solutions were washed with 10% aqueous sodium bicarbonate solution and brine solution, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the residue on silica gel eluting with 10% ethyl acetate in petroleum ether (30-60°C) afforded 204 (294.67 mg; 62.64% yield): ir ($CHCl_3$) 1700 cm^{-1} (C=C); pmr ($CDCl_3$) δ 0.91 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.18 (s, 3H, $\underline{CH_3}$-C(CH)-O-), 1.2 (s, 3H, $\underline{CH_3}$-C(=O)-O-), 3.1-3.7 (br. m, 1H, allylic methine proton) and 1.2-2.7 (m, 12H); ms M^+ 206.1673 (calcd. for $C_{14}H_{22}O$: 206.1673).

10-Hydroxy-1,5,10-Trimethyl-11-oxatricyclo[7.2.1.$0^{4,12}$]undecane (207) and 1,5,10-Trimethyl-11-oxa-$\Delta^{9,10}$tricyclo[7.2.1.$0^{4,12}$]dodecane (208).

To a solution of 194 (178.74 mg, 0.859 mmol) in anhydrous ether (5 ml) was added methyllithium (1.6 mmol,

1.0 ml of 1.6M solution in ether). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 30 min. The reaction mixture was poured into cold saturated aqueous ammonium chloride solution and extracted with ether (2 x 20 ml). The ethereal solutions were washed with brine solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation to give a solid 207 (204.62 mg; 95% yield). Recrystallization from n-hexane afforded pure crystalline 207: m.p. 116-117°C; ir ($CHCl_3$) 3500 cm^{-1} (OH); ms M^+ 224.1682 (calcd. for $C_{14}H_{24}O_2$: 224.1682). (The compound underwent dehydration in $CDCl_3$, therefore the pmr spectrum was not clear). Anal. Calcd. for $C_{14}H_{24}O_2$: C 75.0, H 10.71, O 14.29. Found: C 75.27, H 10.62, O 14.02.

The alcohol 207 (150.0 mg, 0.67 mmol) was dissolved in chloroform (10 ml) and d-10-camphorsulfonic acid (30.0 mg, 0.129 mmol) was added. The resulting solution was stirred at room temperature for 2 hr, poured into water and extracted with chloroform (2 x 20 ml). The chloroform solutions were washed with water, dried with anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by flash chromatography eluting with 10% ethyl acetate in petroleum ether (30-60°C) afforded 208 (135.58 mg; 98.5% yield): ir ($CHCl_3$) 1680 cm^{-1} (C=C); pmr ($CDCl_3$) δ 0.93 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.7 (s, 3H, $\underline{CH_3}$-C(=O)-), 2.7 (d, 1H, J = 8 Hz, C-12 methine proton) and 1.3-2.8 (m, 12H); ms M^+ 206.1573 (calcd. for $C_{14}H_{22}O$:

206.1573).

10-Acetoxy-6,10-dimethylbicyclo[5.3.0]decan-2-one (205 and 209) from 204 and 208.

A solution of 204 (200.0 mg, 0.962 mmol) in distilled dichloromethane (100 ml) was maintained at -78°C and ozone was bubbled through the solution until it turned pale blue in colour. The solution was allowed to warm up to 0°C and methyl sulfide (1 ml) was added. The solution was stirred and allowed to warm up to room temperature. The solvent was removed by flash evaporation and the residue purified by flash chromatography on silica gel eluting with 5% ethyl acetate in petroleum ether (30-60°C) to afford 205 (180.081 mg; 79.32% yield): ir ($CHCl_3$) 1705 (ketone) and 1725 cm^{-1} (ester); pmr ($CDCl_3$) δ 0.99 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.67 (s, 3H, $\underline{CH_3}$-C(=O)-O-), 1.9 (s, 3H, $\underline{CH_3}$-COO-), 1.2-2.8 and 3.1-3.6 (m, 13H); ms M^+ 236.1569 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

Similar treatment of 208 (100.0 mg, 0.485 mmol) with ozone in methylene chloride followed by the work up as described above afforded 209 (86.65 mg; 75% yield): ir ir ($CHCl_3$) 1705 (ketone) and 1725 (ester); pmr ($CDCl_3$) δ 0.95 (3H, $\underline{CH_3}$-CH-), 1.98 (s, 3H, $\underline{CH_3}$-COO-), 1.44 (s, 3H, $\underline{CH_3}$-C(=O)-O-), 3.65 (d, 1H, J = 8 Hz, C-1 methine proton) and 1.2-2.8 (m, 12H); ms M^+ 238.1569 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

6,10-Dimethylbicyclo[5.3.0]dec-10-en-2-one (206 and 210) from 205 and 209.

To a solution of 205 (100.0 mg, 0.420 mmol) in methanol (10 ml) was added 2N methanolic sodium methoxide (1 ml). The resulting solution was stirred at room temperature for 3 hr, poured into water and extracted with ether (2 x 30 ml). The ethereal solutions were washed with brine solution, combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Purification of the residue by flash chromatography on silica gel eluting with 3% ethyl acetate in petroleum ether (30-60°C) afforded 206 (68.85 mg; 92.10% yield): ir ($CHCl_3$) 1680 (ketone) and 1610 cm^{-1} (C=C); pmr ($CDCl_3$) δ 2.02 (s, 3H, $\underline{CH_3}$-$\dot{C}$=), 0.96 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\dot{C}$H-) and 1.2-2.7 (m, 12H); ms M^+ 178.1359 (calcd. for $C_{12}H_{18}O$: 178.1353).

Similarly, treatment of 209 (80.41 mg; 0.338 mmol) with 2N methanolic sodium methoxide (1 ml) followed by isolation and purification of the product by flash chromatography on silica gel eluting with 3% ethyl acetate in petroleum ether (30-60°C) afforded 210 (49.03 mg; 81.5% yield): ir ($CHCl_3$) 1680 (ketone) and 1610 cm^{-1} (C=C); pmr ($CDCl_3$) 0.96 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\dot{C}$H-), 2.02 (s, 3H, $\underline{CH_3}$-$\dot{C}$=) and 1.2-2.7 (m, 12H); ms M^+ 178.1359 (calcd. for $C_{12}H_{18}O$: 178.1353).

1,5-Dimethyl-11-oxa-10-oxo-9-phenylthiotricyclo[7.2.1.$0^{4,12}$]-dodecane (211).

Distilled diisopropylamine (88.7 mg, 0.878 mmol) in dry tetrahydrofuran (5 ml) was stirred at -78°C under a nitrogen atmosphere and n-butyllithium (0.878 mmol, 0.37 ml of 2.4M solution in n-hexane) was added slowly. After 5 min. a solution of the lactone 193 (121.79 mg, 0.586 mmol) in tetrahydrofuran (5 ml) was added and the reaction mixture stirred for 15 min. A solution of diphenyldisulfide (0.205 g, 0.94 mmol) in tetrahydrofuran (5 ml) was added rapidly. The solution was stirred at -78°C for 30 min. and allowed to warm up to 20°C. The reaction mixture was poured slowly into ice-cold water and extracted with ether (3 x30 ml). The ethereal solutions were washed with brine solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation to afford an oily residue. Purification of the product by column chromatography on silica gel eluting with 3-5% ether in n-hexane afforded 211 (138.88 mg; 75% yield). Crystallization from petroleum ether (30-60°C) afforded crystalline 211: m.p. 119-120°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr (CCl_4) δ 7.2-7.5 (m, 5H, aromatic protons), 1.68 (s, 3H, CH_3-$\overset{|}{C}$-O-), 0.89 (d, 3H, J = 5 Hz, CH_3-$\overset{|}{C}$H-) and 1.1-2.4 (m, 13H); ms M^+ 316.1502 (calcd. for $C_{19}H_{24}O_2S$: 316.1484). Anal. Calcd. for $C_{19}H_{24}O_2S$: C 72.15, H 7.59, O 10.13, S 10.13. Found: C 72.04, H 7.79, O 10.22, S 10.02.

10-Hydroxy-11-oxa-9-phenylthio-1,5,10-trimethyltricyclo-[7.2.1.$0^{4,12}$]dodecane (214).

To a solution of the lactone 211 (50.0 mg, 0.158 mmol) in anhydrous ether (15 ml) stirred at -78°C under a nitrogen atmosphere was added methyllithium (0.791 mmol, 0.791 ml of 1.0M solution in ether). The reaction mixture was allowed to warm up to room temperature and maintained at this temperature for 1 hr, poured into cold saturated aqueous ammonium chloride solution and extracted with ether (2 x 30 ml). The combined ethereal solution was dried with anhydrous sodium sulfate, filtered and concentrated. Purification of the residual oily product by flash chromatography on silica gel eluting with 30% ethyl acetate in petroleum ether (30-60°C) afforded an epimeric mixture of 214 (49.89 mg; 95.10% yield): ir ($CHCl_3$) 3605 and 3410 cm^{-1} (OH); pmr (CCl_4) δ 0.81 (3H, CH_3-CH-), 1.3 (s, 3H, CH_3-C(OH)-O-), 1.2 (s, 3H, CH_3-C-O-), 3.32, 3.35 (1H, -O-H), 7.1-7.45 (m, 5H, aromatic protons) and 1.1-2.4 (m, 13H); ms M^+ 332.2707 (calcd. for $C_{20}H_{28}O_2S$: 332.2689).

10-Methoxy-11-oxa-9-phenylthio-1,5,10-trimethyltricyclo-[7.2.1.$0^{4,12}$]dodecane (215).

To a solution of the hemiketal 214 (40.20 mg, 0.121 mmol) in tetrahydrofuran (30 ml) at 0°C under a

nitrogen atmosphere was added sodium hydride (5.808 mg, 0.242 mmol). The reaction mixture was stirred for 20 min. Iodomethane (85.91 mg, 0.605 mmol) was added and the reaction mixture allowed to warm up to room temperature and stirred for 6 hr. The mixture was cooled to 0°C and water (1 ml) was added slowly. The mixture was poured into water and extracted with ether (2 x 30 ml). The ethereal layers were washed with brine solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Purification by flash chromatography on silica gel eluting with 25% ethyl acetate in petroleum ether (30-60°C) afforded 215 (41.03 mg; 98% yield): pmr (CCl_4) δ 0.89 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.2 (s, 3H, $\underline{CH_3}$-C(CH$_3$)-O-), 3.32 (s, 3H, $\underline{CH_3}$-O-), 7.1-7.2 (m, 3H, aromatic protons), 7.4-7.6 (m, 2H, aromatic protons) and 1.1-2.2 (m, 13H). ms M^+ 346.1973 (calcd. for $C_{21}H_{30}O_2S$: 346.1965).

1,5-Dimethyl-11-oxa-10-oxo-9-phenylselenenotricyclo-[7.2.1.$0^{4,12}$]dodecane (216 and 217) from 193 and 194.

To a solution of distilled diisopropylamine (215.073 mg, 2.118 mmol) in dry tetrahydrofuran (5 ml) stirred at -78°C under a nitrogen atmosphere was added n-butyllithium (2.2118 mmol), 0.88 ml of 2.4M solution in n-hexane) via a hydodermic syringe. The solution was stirred for 5 min. A solution of the lactone 193 (367.14 mg, 1.765 mmol) in tetrahydrofuran (5 ml) was slowly added over 5 min period

and then stirred for 20 min. A solution of benzeneselenenyl chloride (473.27 mg, 2.471 mmol) in tetrahydrofuran (5 ml) was added rapidly to the reaction mixture at -78°C and stirred for 5 min. The reaction mixture was poured into a mixture of saturated aqueous sodium bicarbonate, ether and petroleum ether (30-60°C) (1:1:1; 50 ml) and extracted with ether (3 x 30 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined dried, over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. The residue was purified by flash chromatography on silica gel eluting with 5% ethyl acetate in petroleum ether to afford the α-phenylselenenolactone derivative 216 (546.09 mg; 85% yield). Crystallization from n-hexane afforded crystalline 216: m.p. 132-133°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr (CCl_4) δ 0.87 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.64 (s, 3H, $\underline{CH_3}$-C(-O-)), 7.55, 7.48 (both d, 1H each, J = 2 Hz each aromatic protons), 7.1-7.38 (m, 3H, aromatic protons) and 1.3-2.1 (m, 13H); ms M^+ 364.0954 (calcd. for $C_{19}H_{24}O_2Se$: 364:0956). Anal. Calcd. for $C_{19}H_{24}O_2Se$: C 62.64, H 6.59, O 8.79, Se 21.98. Found: C 62.64, H 6.59, O 8.26.

Similar treatment of 194 (183.57 mg, 0.883 mmol) with lithium diisopropylamide and benzeneselenenyl chloride afforded the α-phenylselenenolactone derivative 217 (257.13 mg; 80.0% yield). Crystallization of 217 from n-hexane afforded a crystalline material: m.p. 94-95°C; ir ($CHCl_3$) 1750 cm^{-1} (γ-lactone); pmr (CCl_4) δ 1.52 (s, 3H,

$\underline{CH_3}$-$\overset{|}{C}$-O-), 2.4 (d, 1H, J = 14 Hz, C-12 methine proton), 1.1 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 7.6, 7.53 (both d, 1H each, J = 2 Hz each, aromatic protons), 7.2-7.45 (m, 3H, aromatic protons) and 1.2-2.2 (m, 12H); ms M^+ 364.1064 (calcd. for $C_{19}H_{24}O_2Se$: 364.0956). Anal. Calcd. for $C_{19}H_{24}O_2Se$: C 62.64, H 6.59, O 8.79, Se 21.98. Found: C 63.03, H 6.61, O 8.83.

1,5-Dimethyl-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]dodec-8-ene (219 and 220) from 216 to 217.

To a solution of the α-phenylselenenolactone 216 (420.0 mg, 1.193 mmol) in dichloromethane (50 ml) at 0°C were added pyridine (0.2 ml, 181.7 mg, 2.3 mmol) and hydrogen peroxide (1.1 ml of 30% solution, ~3.58 mmol). The reaction mixture was allowed to warm up to room temperature. After stirring for 1 hr, the mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (3 x 50 ml). The organic layers were washed with 10% aqueous hydrochloric acid (2 x 30 ml) and water. The combined methylene chloride solution was dried with anhydrous magnesium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the product on silica gel eluting with 7% ethyl acetate in petroleum ether afforded 219 (240.883 mg; 98% yield): ir ($CHCl_3$) 1740 (α,β-unsaturated γ-lactone) and 1670 cm^{-1} (C=C); pmr (CCl_4) δ 0.91 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-),

1.36 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.24-2.6 (m, 3H, allylic C-7 and C-12 methine protons, 6.74 (dt, 1H, J = 2 Hz, J' = 14 Hz, =$\overset{|}{C}$-$\underline{H}$) and 1.2-2.0 (m, 8H); ms M^+ 206.1313 (calcd. for $C_{13}H_{18}O_2$: 206.1281).

The α-phenylselenenolactone derivative 217 (210.0 mg, 0.597 mmol) was similarly treated with hydrogen peroxide (1.7898 mmol) in methylene chloride to afford the α,β-unsaturated lactone 220 (110.68 mg; 90% yield) ir ($CHCl_3$) 1740 (α,β-unsaturated γ-lactone) and 1670 cm^{-1} (C=C); pmr (CCl_4) δ 6.67 (m, 1H, C-8 vinylic proton), 3.17 (br. m, 1H, C-12 allylic methine proton), 1.46 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 1.1 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-) and 1.2-2.2 (m, 8H); ms M^+ 206.1307 (calcd. for $C_{13}H_{18}O_2$: 206.1281).

1,5-Dimethyl-8,9-epoxy-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]-dodecane (224 and 225) from 219 and 220.

To a solution of 219 (581.56 mg, 2.82 mmol) in methanol-tetrahydrofuran (1:1; 70 ml) stirred at room temperature was added hydrogen peroxide (0.88 ml of 30% solution, ~7.15 mmol). 3N aqueous sodium hydroxide solution (0.94 ml) was added slowly over 15 min period by means of a hypodermic syringe. The temperature of the reaction mixture was maintained at 15-25°C throughout the reaction period as higher temperatures drastically reduced the yield of the product. The reaction mixture was stirred for 8 hr, poured into cold water and extracted with ether (3 x 50 ml). The ethereal

solutions were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the residue on silica gel eluting with 15% ethyl acetate in petroleum ether (30-60°C) afforded an oily product 224 (595.39 mg; 95% yield). Crystallization from n-hexane afforded crystalline 224: m.p. 124-125°C; ir ($CHCl_3$) 1775 cm^{-1} (α,β-epoxy lactone); pmr ($CDCl_3$) δ 2.4 (t, 1H, J = 1 Hz, C-8 oxirane proton), 2.11 (d, 1H, J = 6 Hz, C-12 methine proton), 1.54 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 0.94 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-) and 1.1-2.5 (m, 10H); ms M^+ 222.1241 (calcd. for $C_{13}H_{18}O_3$: 222. 1228). Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.27, H 8.11, O 21.62. Found: C 70.11, H 8.08, O 21.88.

Similar treatment of 217 (100.0 mg, 0.485 mmol) with hydrogen peroxide and sodium hydroxide afforded 225 (99.59 mg; 92.50% yield): ir ($CHCl_3$) 1770 cm^{-1} (γ-lactone); pmr ($CDCl_3$) δ 1.02 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 1.48 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.5 (t, 1H, J = 3 Hz, C-8 oxirane proton) and 1.2-2.7 (m, 11H); ms M^+ 222.1241 (calcd. for $C_{13}H_{18}O_3$: 222.1228).

1,5-Dimethyl-8-methoxy-11-oxa-10-oxotricyclo[7.2.1.$0^{4,12}$]-dodecane (223).

To a solution of the unsaturated lactone 219 (40.98 mg, 0.199 mmol) in methanol (5 ml) was added 2N methanolic sodium methoxide (0.2 ml). The resulting solution was

stirred at room temperature for 48 hr. The mixture was poured into water and extracted with ether (2 x 20 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Column chromatography of the residue on silica gel eluting with 25% ether in n-hexane afforded 223 (19.04 mg; 37.35% yield): ir ($CHCl_3$) 1750 (γ-lactone); pmr (CCl_4) δ 0.90 (3H, CH_3-CH-), 2.81 (t, 1H, J = 6 Hz, C-9 methine proton), 3.30 (m, 1H, -CH-OCH_3), 3.34 (s, 3H, -CH-OCH_3) and 1.2-2.2 (m, 11H); ms M^+ 238.1571 (calcd. for $C_{14}H_{22}O_3$: 238.1560).

8,9-Epoxy-10-hydroxy-11-oxa-1,5,10-trimethyltricyclo-[7.2.1.$0^{4,12}$]dodecane (226) from 224.

Methyllithium (4.96 mmol, 2.48 ml of 2.0M solution in ether) was added to a solution of the epoxylactone 224 (500.0 mg, 2.25 mmol) in anhydrous ether (100 ml) stirred at -78°C under a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 20 min and poured into ice-cold water with stirring. The ethereal layer was separated and the aqueous layer extracted with ether (2 x 50 ml). The organic layers were washed with saturated aqueous sodium chloride solution, combined, dried with anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the residue on silica

gel eluting with 25% ethyl acetate in petroleum ether (30-60°C) afforded an epimeric mixture of the hemiketals 226 (520.90 mg; 98% yield): ir ($CHCl_3$) 3520 and 3600 cm^{-1} (OH); pmr (CCl_4) δ 2.96, 3.13 (both t, 1H total, J = 5 Hz each, C-8 oxirane proton), 1.32, 1.46 (both s, 3H total, $\underline{CH_3}$-$\overset{O-}{\overset{|}{C}}$-O-), 1.26, 1.04 (both s, 3H total, $\underline{CH_3}$-$\overset{|}{C}$-O-), 0.94 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-) and 1.2-2.4 (m, 11H); ms m/e (M-18) 220.1466 (calcd. for $C_{14}H_{20}O$: 220.1508).

8,9-Epoxy-10-methoxy-11-oxa-1,5,10-trimethyltricyclo-[7.2.1.$0^{4,12}$]dodecane (227) from 226.

A solution of the hemiketal 226 (500.0 mg, 2.12 mmol) in anhydrous tetrahydrofuran (20 ml) was added slowly to a stirred suspension of sodium hydride (122.03 mg, 2.54 mmol; 50% sodium hydride in mineral oil) in tetrahydrofuran (30 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min. and iodomethane (890.40 mg, 6.36 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 6 hr. The resulting mixture was poured slowly into ice-cold water and extracted with ether (3 x 50 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the residue on silica gel eluting with 20% ethyl acetate in petroleum ether (30-60°C) afforded the ketal 227

(529.46 mg; ~100% yield): pmr (CCl_4) δ 3.36 (d, 1H, J = 6 Hz, C-12 methine proton), 3.14 (s, 3H, -O-CH_3), 2.92 (t, 1H, J = 3 Hz, C-8 oxirane ring proton), 1.47 (s, 3H, CH_3-C(=O)-O-), 1.18 (s, 3H, CH_3-C-O-), 0.91 (d, 3H, J = 5 Hz, CH_3-CH-) and 1.2-2.5 (m, 11H); ms M^+ 252.1007 (calcd. for $C_{15}H_{24}O_3$: 252.1000).

8,9-Epoxy-10-methoxy-11-oxa-1,5,10-trimethyltricyclo-[7.2.1.$0^{4,12}$]dodecane (228) from 225.

Methyllithium (0.892 mmol, 0.446 ml of 2.0M solution in ether) was added to a solution of the epoxylactone 225 (90.0 mg, 0.405 mmol) in anhydrous ether (10 ml) stirred at -78°C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min , poured into ice-cold water and extracted with ether (3 x 20 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation to give the hemiketal 227a (96.48 mg, ~100% crude yield). Without purification this compound was dissolved in dry tetrahydrofuran (10 ml) and the solution stirred at 0°C under a nitrogen atmosphere. To this solution were added, 20 min. apart, sodium hydride (23.32 mg; 0.486 mmol; 50% dispersion in mineral oil), and iodomethane (287.55 mg, 2.025 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 6 hr. The reaction mixture was poured

slowly into cold water and extracted with ether (3 x 20 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Flash chromatography of the residue on silica gel eluting with 20% ethyl acetate in petroleum ether (30-60°C) afforded 228 (83.69 mg; 82% yield): pmr (CCl_4) δ 0.91 (d, 3H, J = 5 Hz, $\underline{CH_3}$-CH-), 1.25 (s, 3H, $\underline{CH_3}$-C(O-)-), 1.47 (s, 3H, $\underline{CH_3}$-C(O-)-O-CH_3), 3.16 (s, 3H, $\underline{CH_3}$-O-), 2.88 (t, 1H, J = 5 Hz, C-8 oxirane ring proton) and 1.2-2.3 (m, 11H); ms M^+ 252.1007 (calcd. for $C_{15}H_{24}O_3$: 252.1000).

11-Oxa-1,5,10-trimethyl-$\Delta^{9,10}$tricyclo[7.2.1.$0^{4,12}$]dodecane-8-one (229) from 227.

A solution of the epoxide 227 (500.0 mg, 1.984 mmol) in ether (100 ml) was stirred at 0-5°C under a nitrogen atmosphere and boron trifluoride etherate (1.5 ml) was added. The resulting solution was stirred at 0-5°C for 2 hr, poured into cold saturated aqueous sodium bicarbonate solution and the ethereal layer separated. The aqueous phase was extracted with ether (100 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered, and the solvent removed by flash evaporation. Purification of the residue by flash chromatography on silica gel eluting with 15% ethyl acetate in petroleum ether (30-60°C) afforded 229

(330.0 mg; 75% yield): ir ($CHCl_3$) 1660 (ketone) and 1580 cm^{-1} (C=C); pmr (CCl_4) δ 1.32 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$-O-), 2.12 (s, 3H, $\underline{CH_3}$-$\overset{\|}{C}$-O-), 0.95 (d, 3H, J = 5 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-) amd and 1.1-2.5 (m, 11H); ms M^+ 220.1466 (calcd. for $C_{14}H_{20}O_2$: 220.1455).

11-Oxa-1,5,10-trimethyl-$\Delta^{9,10}$tricyclo[7.2.1.$0^{4,12}$]dodecan-8-one (229) from 226.

A solution of the epoxy-hemiketal 226 (250.0 mg, 0.992 mmol) in ether (50 ml) was stirred at 0-5°C under a nitrogen atmosphere and boron trifluoride etherate (0.75 ml) was added. The resulting solution was stirred at 0-5°C for 2 hr, poured into cold saturated aqueous sodium bicarbonate solution and the ethereal layer separated. The aqueous layer was extracted with ether (2 x 40 ml). The ethereal layers were washed with saturated aqueous sodium chloride solution, combined, dried over anhydrous sodium sulfate, filtered and the solvent removed by flash evaporation. Purification of the residue by flash chromatography on silica gel eluting with 15% ethyl acetate in petroleum ether (30-60°C) afforded 229 (109.13 mg; 50% yield). The spectral data of 229 has already been discussed (vide supra).

REFERENCES

1. A.R. Penfold, J. Proc. Roy. Soc., New South Wales, 60, 104 (1926).
2. A.E. Bradfield, A.R. Penfold and J.L. Simonsen, J. Proc. Roy. Soc., New South Wales, 66, 2744 (1932).
3. A.E. Bradfield, A.R. Penfold and J.L. Simonsen, J. Proc. Roy. Soc., New South Wales, 67, 200 (1933).
4. A.J. Birch, D.J. Collins and A.R. Penfold, Chem. and Ind., 1773 (1955).
5. D.J. Collins, J. Chem. Soc., 531 (1959).
6. R.P. Hildebrand and M.D. Sutherland, Aust. J. Chem., 12, 436 (1959).
7. T.G.H. Jones and S.E. Wright, Univ. Queensland Papers, Dept. of Chem. 1, No. 27, 7 pp (1946).
8. D.H.R. Barton and G.S. Gupta, Proc. Chem. Soc., 308 (1961).
9. D.H.R. Barton G.S. Gupta, J. Chem. Soc., 1961 (1962).
10. R.C. Cookson and N.S. Wariyar, J. Chem. Soc., 2302 (1956).
11. A.J. Birch, D.J. Collins, A.R. Penfold and J.P. Turnbull, J. Chem. Soc., 792 (1962).
12. S. Ito, H. Takeshita, M. Hirama and Y. Fukazawa, Tetrahedron Letters, 9 (1972).
13. S. Itô, H. Takeshita and M. Hirama, Tetrahedron Letters, 1775 (1972).

14. M. Palmade, P. Poulle, J. Streith and G. Ourisson, Bull. Soc. Chim. France, 1950 (1963).

15. E. Rodriquez, G.N. Towers and J.C. Mitchell, Phytochem., 15, 1573 (1976).

16a. T. Sato, H. Minato and H. Koyama, Chem. Commun., 363 (1966).

16b. R.A. Lucas, J. Org. Chem., 29, 1549 (1964).

17. S.M. Kupchan, M.A. Eakin and A.M. Thomas, J. Med. Chem., 14, 1147 (1971).

18. E.L. Elliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, Conformational Analysis, pp 200-210 (1965). Inter Science Publishers, New York.

19. J.L. Nelson, C.C. Cobb and A.A. Frost, J. Chem. Phys., 60, 712 (1974).

20. J.B. Hendrickson, J. Amer. Chem. Soc., 83, 4537 (1961).

21. J.B. Hendrickson, J. Amer. Chem. Soc., 84, 3355 (1962).

22. J.B. Hendrickson, J. Amer. Chem. Soc., 89, 7047 (1967).

23. J.D. Roberts and M. Christl, J. Org. Chem., 37, 3443 (1972).

24. H.L. Strauss, T.C. Rounds, H.M. Picket and D.F. Bocian, J. Amer. Chem. Soc., 97, 687 (1975).

25. D.H.R. Barton, P. de Mayo and M. Shafig, J. Chem. Soc., 929 (1957).

26. C.H. Heathcock, R. Ratcliff and J. Van, J. Org. Chem., 37, 1796 (1972).

27. Y. Mazur and M. Nussim, J. Amer. Chem. Soc., 83, 3911 (1961).

28. H. Minato, Chem. Abstracts, 67, 54023 p (1967).

29. G. Buchi, W. Hofheinz and J.W. Paukstelis, J. Amer. Chem. Soc., 88, 4113 (1966).

30. G. Buchi, W. Hofheinz and J.W. Paukstelis, J. Amer. Chem. Soc., 91, 6473 (1969).

31. G.H. Posner, G.L. Loomis, R.D. Mittal, W.J. Frazee, D.M. Schmidt and K.A. Babiak, Tetrahedron Letters, 4213 (1978).

32. O.P. Vig, S.S. Bari, S.D. Sharma and M. Lal, Ind. J. Chem. B., 16, 109 (1978).

33. J.B. Hendrickson, C. Ganter, D. Dorman and H. Link, Tetrahedron Letters, 2235 (1968).

34. R.A. Kretchner and W.J. Thompson, J. Amer. Chem. Soc., 98, 3379 (1976).

35. J.A. Marshall and N.H. Andersen, Tetrahedron Letters, 1219 (1967).

36. J.A. Marshall, N.H. Andersen and C.J. Porter, J. Org. Chem., 35, 186 (1970).

37. N.H. Andersen and F.A. Golec Jr., Tetrahedron Letters, 3783 (1977).

38. M.F. Semmelhack, A. Yamashita, J.C. Tomesh and K. Hrotsu, J. Amer. Chem. Soc., 100, 5565 (1978).

39. M. Yamasaki, J.C.S. Chem. Commun., 606 (1972).

40. K.E. Harding and W.D. Nash, Syn. Commun., 7, 19 (1977).

41. P.A. Grieco, Y. Ohfune, G.L.S. Wang and G. Majetich, J. Amer. Chem. Soc. 99, 7397, (1977).

42. P.A. Grieco, Y. Ohfune, G.L.S. Wang and G. Majetich, J. Amer. Chem. Soc., 100, 5946 (1978).

43. J.B. Hendrickson and R.K. Boeckman, J. Amer. Chem. Soc., 93, 1307 (1971).

44. G.L. Buchanan and G.A.R. Young, Chem. Commun., 643 (1971). 643 (1971).

45. H. Hikino and P. de Mayo, J. Amer. Chem. Soc., 86 3582 (1964).

46. H.J. Liu, Syn. Commun., 4, 237 (1974).

47. P.G. Bauslaugh, Synthesis, 287 (1970).

48. P. de Mayo, Accounts of Chemical Research, 4, 41 (1971).

49. H.J. Liu and S.P. Lee, Tetrahedron Letters, 3699 (1977).

50. H.J. Liu, unpublished work (1975).

51. H.J. Liu and Linda A. Corleto, Unpublished work (1976).

52. E.J. Corey, R. Greenwald and M. Chaykovsky, J. Org. Chem., 28, 1128 (1963).

53. D. Alder and G. Stein, Ann. 504, 216 (1933).

54. Michael H. Karger and Yehuda Mazur, J. Amer. Chem. Soc., 90, 3878 (1968).

55. S.M. Kupchan, Y. Shizuri, R.L. Baxter and H.R. Haynes, J. Org. Chem., 42, 347 (1977).

56. D.H.R. Barton, J.T. Pinkey and R.J. Wells, J. Chem. Soc., 2158 (1964).

57. R.A. Lucos, R.G. Smith and L. Dorfman, J. Org. Chem., 29, 2101 (1964).

58. E.H. White, S. Eguchi and J.N. Marx, Tetrahedron, 25, 2009 (1969).

59. cf J.N. Marx and M. McGaughey, Tetrahedron, 28, 3583 (1972).

60. L. Skattebøl, E.R.H. Jones and M.C. Whitting, Org. Syn., Coll. Vol. 4, 792 (1963).

61. J.W. Huffman and P.G. Arapakos, J. Org. Chem., 30, 1604 (1965).

62. M.M. Midland, J. Org. Chem., 40, 2250 (1975).

63. H.B. Kagan, A. Marquett and J. Jacques, Bull. Chem. Soc., 1079 (1960).

64. R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A. Ives and R.B. Kelly, J. Chem. Soc., 1131 (1957).

65. R.B. Woodward, I.W. Patcher and M.L. Scheinbaum, J. Org. Chem., 36, 1137 (1971).

66. H. Gilman, W. Langham and F.W. Moore, J. Amer. Chem. Soc., 62, 2327 (1940).

67. T. Mukaiyama, K. Banno and K. Narasaka, J. Amer. Chem. Soc., 96, 7503 (1974).

68. B.M. Trost, T.N. Salzmann and K. Hiroi, J. Amer. Chem. Soc., 98, 4887 (1976).

69. H.J. Reich, J.M. Renga and Ieva L. Reich, J. Amer. Chem. Soc., 97, 5434 (1975).

70. U. Mende, B. Radiichel, W. Skuballa and H. Vorbriiggen, Tetrahedron Letters, 629 (1975).

71. E.J. Corey and R.L. Dawson, J. Amer. Chem. Soc., 85, 1782 (1963).

72. C.H. De Puy and K.L. Eilers, Org. Syntheses, 42, 38 (1962).

73. V.M. Mićoćovic, Org. Syntheses, Coll. Vol. II, 264 (1943).